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THERAPEUTIC USE OF THE CONCENTRATED STREPTOCOCCUS SERUM OF THE NEW YORK STATE DEPARTMENT OF HEALTH

IN PATIENTS WITH INFECTIONS OF THE EAR, NOSE AND THROAT

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Inflammatory disease of the upper respiratory region is exceedingly common and in a considerable portion of the patients hemolytic streptococci are present on the mucous membrane in abundance and are evidently etiologically related to the disorder. When the infection extends to the middle ear, the mastoid, the bronchi and the adjacent parenchyma of the lung or to the blood stream, one is not infrequently able to detect streptococci in pure culture in these new situations, a circumstance which offers strong evidence implicating the streptococcus as an important inflammatory agent at the original site, where it had been associated with other microbes. The use of streptococcus serum in the treatment of infections of the upper respiratory tract seems to have been somewhat neglected, except when these inflammations have been associated with the clinical manifestations leading to a diagnosis of erysipelas or of scarlet fever. We are inclined to a somewhat different point of view and favor employing streptococcus serum whenever there is good reason to believe that virulent streptococci are concerned in the causation of dangerous inflammation, regardless of the particular classic clinical entity under guise of which it appears. This point of view may be more clearly elucidated after a consideration of the individual patients.

Among our twenty-six patients treated with the concentrated serum of the laboratory of the New York State Department of Health there are eight which have been allocated to this category of infections of the ear, nose or throat, although one of them apparently had his initial

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The patients whose records are utilized in this paper were treated in the clinical services of the following physicians: Dr. A. G. De Sanctis, Dr. S. C. Glasgow, Dr. J. E. Hutton and Dr. D. Macpherson.

lesion low in the esophagus. The serum treatment was initiated at an advanced stage of the disease as a rule. Of the eight patients, two died and six survived.

REPORT OF CASES

CASE 1.—S. W., a girl, aged 4 months, became ill on March 7, 1933, with a swollen lymph node in the neck and high fever. On admission to the hospital on March 11, severe purulent rhinitis and bilateral purulent otitis media were recognized. The abridged clinical record is shown in chart 1. Spinal tap immediately after admission yielded a normal spinal fluid. The right ear drum was incised on March 13. On March 16 a blood culture was taken, and 20 cc. of human blood was given by intramuscular injection. The blood culture became positive on March 17, showing eighty-five colonies of hemolytic streptococci per cubic centimeter of blood. On this day the left middle ear was opened, and one-half ampule (10,000 units) of the concentrated streptococcus serum was given by intramuscular injection. On March 18 left mastoidectomy was done, with ligation of the left jugular vein and removal of a thrombus from the left lateral sinus. A transfusion was given before the operation and another on March 20. On March 21 there was recognized pneumonia on the right side, and the left arm became blue and

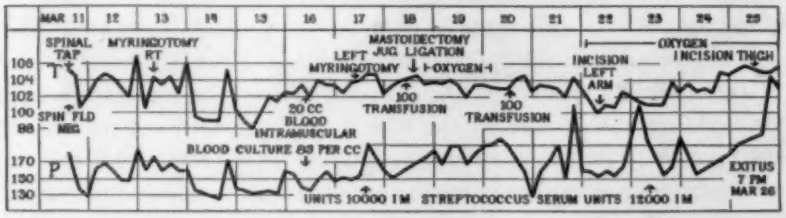

Chart 1.—Abridged clinical record of S. W., a girl, aged 4 months. This patient had a positive blood culture taken on March 16. On the following day 10,000 units of serum was given by intramuscular injection. No further serum was given until March 23, when another dose of 12,000 units was given intramuscularly. In the interval there was an operation on the mastoid with ligation of the jugular vein on March 18. The child died on March 26.

tensely swollen. Aspiration of the arm was performed and an incision made on March 22, a large amount of purulent exudate containing streptococci being evacuated. Another intramuscular injection of the streptococcus serum, 12,000 units, was administered on March 23. On the next day the site of the injection on the left buttock appeared necrotic. An abscess of the right thigh was opened on March 25. Oxygen was given on March 18 and 19 and again from March 22 until death on March 26.

Necropsy revealed, in addition to the disease of the left mastoid region, active purulent mastoiditis on the right side and extending from it a dissecting abscess (von Bezold) along the carotid sheath into the mediastinum to the soft tissues about the shoulder and down the left arm, septic infarcts of both lungs with fibrinopurulent pleurisy on the right side, metastatic abscesses in both thighs and the left buttock and septic changes in the various organs. The cardiac valves were normal.

CASE 2.—A. G., a boy, aged 11 months, had his right ear drum incised on March 19, 1933, and again on March 22. A purulent discharge continued until about March 25, and during this time the temperature ranged from 101 to 103 F.

On March 31 the mother noticed that the right lower extremity remained flexed, and attempts to straighten it evidently caused pain. From March 30 to April 9 the temperature observed at home ranged from 100 to 101 F. The baby was admitted to the hospital at 11 a. m. on April 9, on account of the deformity of the leg. The abridged clinical record is shown in chart 2.

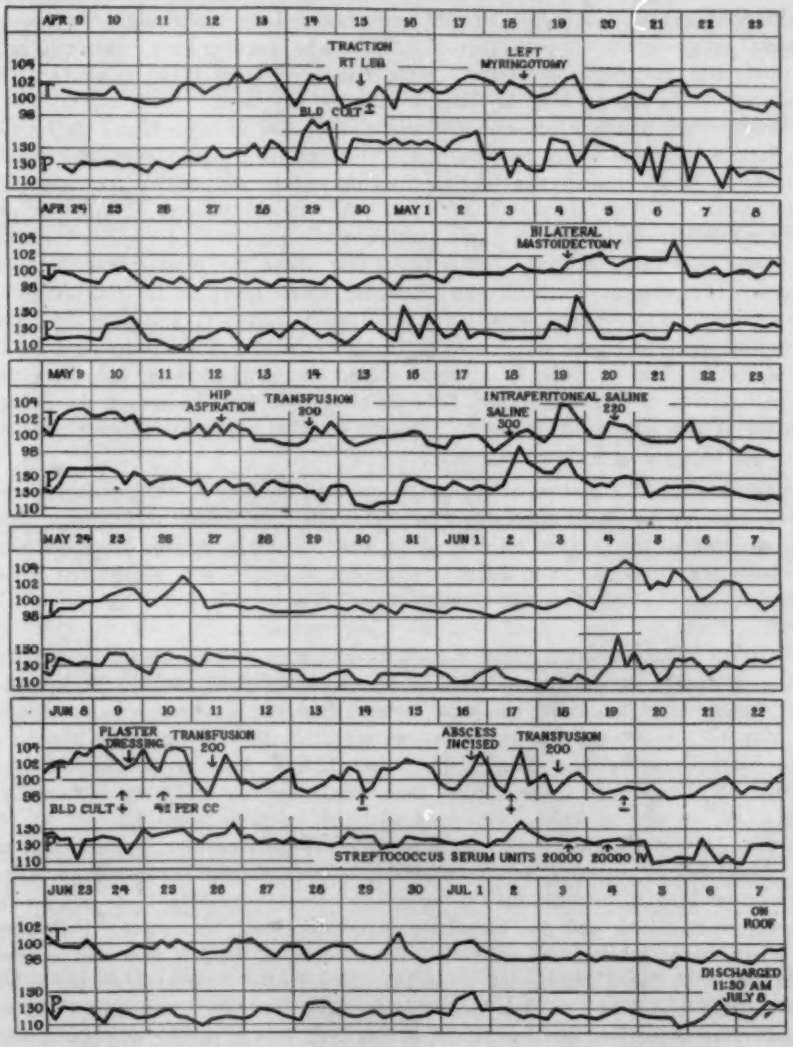

Chart 2.—Abridged clinical record of A. G., a boy, aged 11 months. The illness began with otitis media about the middle of March. Subsequently there was some disability of the right leg, for which the patient was admitted to the hospital. Bilateral mastoidectomy was performed on May 4. A positive blood culture was obtained for the first time on June 9. The serum was administered on June 18 and June 19, a total of 40,000 units intravenously. The child was discharged on July 8 in good condition. There was no serum reaction.

Examination on admission disclosed little in addition to the foregoing data. The flexion at the right hip and knee was not associated with recognizable swelling, redness or induration. Roentgenologic study, however, revealed evidence of marked synovial distention of the right hip joint on April 9 and on April 18 destructive arthritis and epiphysitis, apparently of metastatic origin. The right ear was no longer draining, but on April 18 the left ear drum was incised to facilitate drainage, which had already been initiated spontaneously. On May 4 bilateral mastoidectomy was performed. There was mucopurulent exudate in each mastoid, and hemolytic streptococci were recovered from these exudates. The aspiration of the hip on May 12 failed to disclose any fluid.

Without any apparent reason there was a sharp rise in temperature on June 4. On June 9 the right lower extremity was enclosed in a plaster dressing, and on this day a blood culture was taken. This proved to be positive for hemolytic streptococci. Another blood culture taken on June 10 yielded 42 colonies per cubic centimeter of blood. A blood culture taken on June 14 remained sterile. On June 16 a large abscess on the back, just above the plaster dressing, was opened. This contained streptococci. A blood culture taken on the following day was positive. Transfusions were given on May 14, June 11 and June 18. The concentrated streptococcus serum was given intravenously, 20,000 units on June 18 and a similar dose on June 19. Convalescence was gradual from this time, and the patient was discharged on July 8, being allowed to bear weight on the plaster dressing at this time. There was no urticaria or other evidence of serum sickness following the injection of the serum.

Case 3.—M. S., a girl, aged 4 years, became ill on May 5, 1933, with rhinitis. Three days later a small abscess on the right side of the nose was lanced. She was admitted to the hospital on May 9, at which time the nostrils were occluded by edema and congestion, and many enlarged lymph nodes were recognized in the neck, especially along the left carotid chain. The abridged clinical record is shown in chart 3.

A blood culture taken on May 9 gave a positive growth of hemolytic streptococci. A transfusion was given on May 11. Roentgenologic study revealed capsular distention of the right hip joint without evidence of changes in the bones. On May 12 the concentrated streptococcus serum of the laboratory of the New York State Department of Health was injected, first into the skin, revealing a positive sensitiveness to horse serum, then subcutaneously and then intramuscularly. One ampule of 20,000 units was administered daily from May 12 to 16, inclusive. A blood culture taken on May 16 was again positive, the colonies on the plates being recorded as "innumerable." An eruption of small pustules appeared on May 19, and the patient became irrational. On May 22 an abscess on the heel was incised, and pus containing streptococci was evacuated. Following this there were cyanosis and delirium. An abscess of the left arm was opened on May 27. A blood culture taken on May 29 revealed 3 streptococci per cubic centimeter of blood, and another blood culture taken on May 31 remained sterile. Transfusions were given on May 11, 17, 24 and June 7. The patient was discharged on June 12.

Progress at home was not satisfactory, and the child was returned to the hospital on June 16 because of pain in the left hip. Roentgenologic study revealed osteomyelitis of the left femur. This was treated surgically without use of further serum, and the patient was finally discharged, improved, on August 10.

Among the unusual features of this record, one may mention the early recognition of the bacteremia, the sensitiveness of the patient to

horse serum, the effective desensitization, the absence of subsequent serum sickness and the eventual survival of the patient. We are inclined to think that intravenous injection of the later doses of serum might have been better than use of the intramuscular route. The wisdom of further injections of the serum may be open to debate. We are inclined to favor larger doses continued over a longer period for an actual streptococcic bacteremia. Possibly the unfortunate sequel of osteomyelitis might thus have been avoided. One should note that the right hip joint appeared to be threatened early but that the late bone lesion appeared in the left femur.

CASE 4.—M. C., a boy, born on Dec. 13, 1928, had been subject to vomiting since the age of 2 weeks. On March 12, 1931, he swallowed a cherry stone, and subsequent to that no solid food was retained and even liquids were regurgitated

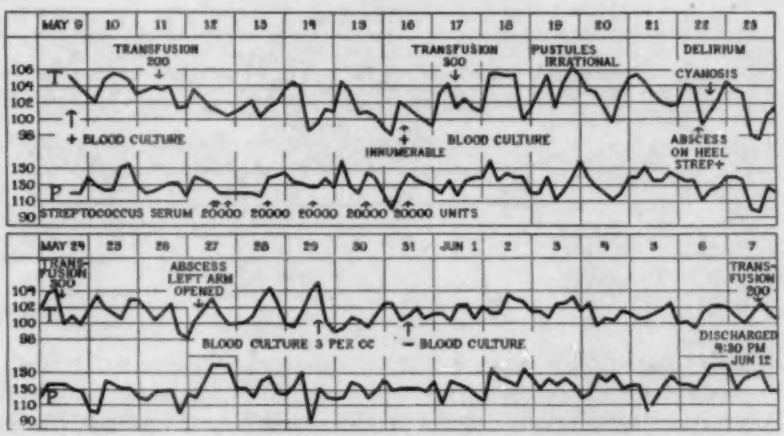

Chart 3.—Abridged clinical record of M. S., a girl, aged 4 years. The illness started with an infection of the upper respiratory tract. A blood culture taken on the day of admission was positive. Serum was administered on May 12, 13, 14, 15 and 16, a total of 100,000 units. The patient had a stormy convalescence, but was discharged on June 12. She returned to the hospital on June 16 with osteomyelitis of the left femur and was finally discharged improved on August 10. It appears that the amount of serum given was somewhat too small in this case.

frequently. On March 24 he came to the hospital and at that time there was discovered an esophageal stricture 8½ inches (21.5 cm.) from the upper incisor teeth with an enormous dilatation above it and a foreign body, recognized as a cherry stone, caught in the stricture. After this he returned to the hospital at frequent intervals for dilation of the stricture. On March 9, 1933, he came for his usual treatment, consisting of esophagoscopy and dilation with bougies. On March 23 he came for another treatment, but at this time the esophagoscopic examination revealed ulceration at the cardiac end of the stricture. Bougies were therefore not passed, but a Senn gastrostomy was performed on March 28 in order to favor healing of the ulcer. This healing progressed favorably, so that the stricture of the esophagus was dilated from below through the gastrostomy

on April 13 and again on April 20. The child was sent home, but returned again on April 27 for a third dilation from below. He came again on May 4 for a dilation, but because he had been taking food by mouth the treatment was canceled and he was sent home at 1 p. m. on May 5, his morning temperature having been 99.4 F. On the same day he was readmitted to the hospital at 4:10 p. m., severely ill, with a temperature of 104.2 F., which rose to 105.4 F. at 8 p. m.

The abridged clinical record is shown in chart 4. Spinal tap at 9 p. m. on May 5 yielded a negative fluid, and a blood culture taken on May 9 remained sterile. However, the blood culture taken on May 11 gave a growth of hemolytic streptococci, and blood cultures on May 13 and 16 were also positive, the latter showing 52 colonies per cubic centimeter of blood. The concentrated streptococcus serum was given intravenously, one ampule daily from May 12 to 16, inclusive, the total amounting to 100,000 units. The patient was given a transfusion on May 12 and 17. There was no perceptible response to these therapeutic measures, and death took place early on the morning of May 22.

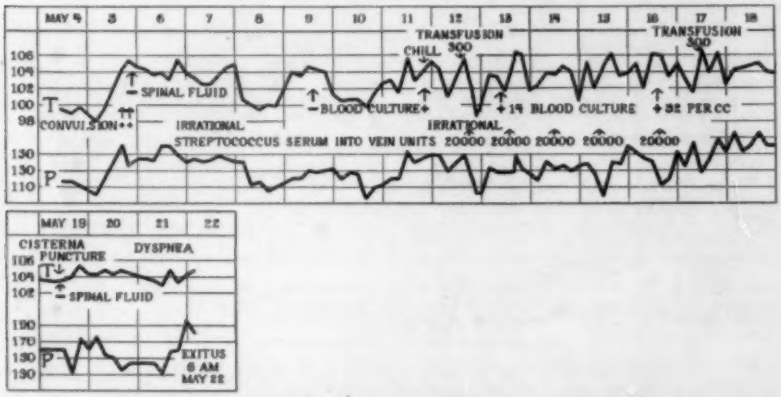

Chart 4.—Abridged clinical record of M. C., a boy, aged 5 years. This child was under treatment for stricture of the esophagus. On May 5 there evidently developed a severe infection extending from the esophageal stricture. A blood culture taken on May 11 was positive. Serum was given on May 12, 13, 14, 15 and 16, a total of 100,000 units. The child died on May 22. Necropsy revealed bilateral empyema and vegetative endocarditis, apparently taking origin from the ulcerated esophageal stricture.

Necropsy disclosed: complete ulceration of the esophagus throughout the constricted portion which extended from the level of the uppermost part of the aortic arch to the cardia, with marked fibrous thickening of the wall of the esophagus; mediastinal lymphadenitis; bilateral empyema; acute vegetative lesions on the mitral, aortic and tricuspid valves, and multiple septic infarcts of both lungs, along with other signs of general sepsis.

Case 5.—F. C., a girl, aged 6 years, received a bruise in the lower abdominal region on hitting the corner of a table on Jan. 14, 1933, and this was followed by appearance of blood at the vulval outlet. Two days later an appendectomy was performed, and the postoperative course was uneventful until the ninth day, when the temperature rose to 104 F. and the pharynx was found to be inflamed. After four days the fever subsided, but the sore throat and tenderness of the

muscles of the neck persisted. The child was taken home on January 31. She had chills with a rise of temperature to 102 F. every two or three days. Between times she appeared well except for vague pains in the joints and stiffness of the neck. On February 12, at noon, she had a chill with a rise in temperature to 104 F. By evening the temperature was normal. The evening specimen of urine was filled with blood. The patient was admitted to the Post-Graduate Hospital for the first time on February 14, at which time there were recognized slight coryza, a reddened pharynx and enlarged cervical lymph nodes.

The abridged hospital record is shown in chart 5. On February 15, at 1 p. m., there was a chill followed by a rise in temperature to 104 F. A blood culture taken on February 16 produced a growth of hemolytic streptococci in twenty-four hours. When this was recognized on February 17, another blood culture was taken, bacteriologic examination of the urine was undertaken and one ampule of concentrated streptococcus serum was given by intramuscular injection. On the next day a transfusion was given, and the dose of serum was repeated. A blood culture taken on February 20 remained sterile. There were no further chills. After February 28 the highest temperature observed was 99.6 F. The patient was discharged on March 7, without a definite understanding having been reached of the disorder from which she seemed to have recovered. The traumatic factor in the history seems problematic; the possible influence of the appendectomy is

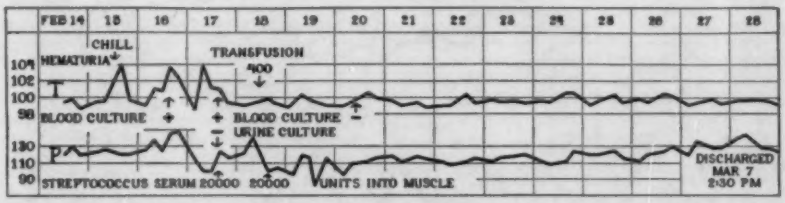

Chart 5.—Abridged clinical record of F. C., a girl, aged 6 years. This child was admitted on account of hematuria. A positive blood culture was obtained on February 16 and again on February 17. The serum was administered on February 17 and February 18, a total of 40,000 units. The recovery was very prompt.

uncertain. Perhaps inflammation of the upper respiratory tract with extension of streptococcic infection to the lymphatics and to the blood stream, complicated by hemorrhagic nephritis, may fit the situation. At any event, the improvement of the patient following the injection of the serum and the transfusion was dramatic.

Case 6.—E. T., a girl, aged 20, was admitted to the hospital on April 6, 1932 (chart 6), and a right mastoidectomy with exposure of the lateral sinus was performed. On April 10 the patient complained of frontal headache, and on April 11 the temperature continued to mount, reaching 105 F. at 4 p. m. A blood culture taken at 1:30 p. m. on this day showed a positive growth of hemolytic streptococci. Spinal tap at 7 p. m. on April 11 yielded a normal spinal fluid. A transfusion was given at 9 p. m. On April 12, at 5 a. m., there was a chill lasting twenty minutes with a rise in temperature to 106.4 F. On this day the right lateral sinus was again exposed, and free bleeding was obtained from its upper portion. Incision was then made in the neck; the right jugular vein and its facial branch were ligated and severed. On April 15 an area of erysipelas was recognized about the right ear. The patient complained of abdominal pain and difficulty in swallowing. On April 16 the area of redness had extended to include the

eyelids and the lower portion of the forehead. It was edematous with a sharply defined margin. Erysipelas antitoxin (commercial), 500,000 skin units, was given subcutaneously on this day. The patient was very weak and unable to swallow fluids. On this account a duodenal tube was inserted for about twenty-four hours. A blood culture taken on April 18 again gave positive growth of hemolytic streptococci. On April 26 the blood culture was positive, yielding 16 colonies per cubic centimeter of blood. On April 28 the patient was cyanotic, with a feeble pulse, and was apparently in a desperate condition. Transfusion was given on April 29. The concentrated streptococcus serum of the New York State Department of Health was given for the first time on April 30, first a minute intracutaneous dose at 1:30 p. m., which revealed a marked hypersensitiveness. This was followed by an intravenous dose of 1 cc. at 2 p. m., and at 5 p. m. an intravenous dose of 3 cc. The patient had a chill lasting thirty minutes. The serum treatment was continued, 5 cc. on May 1, two doses of 5 cc. each on May 2 and a final dose of 5 cc. on May 3, all intravenously. The total amount was 60,000 units,

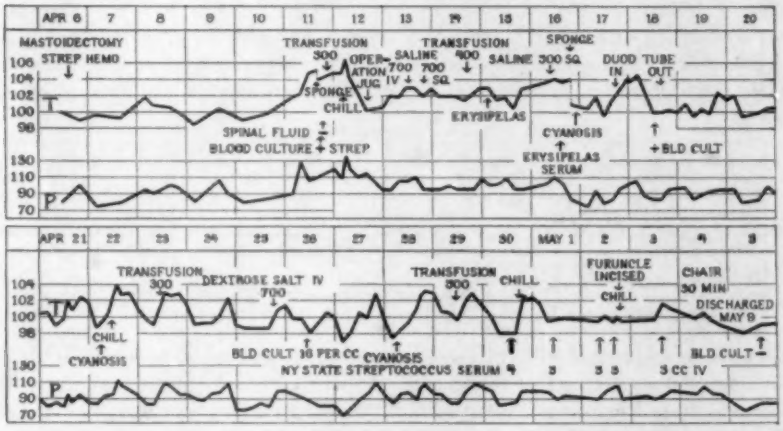

Chart 6.—Abridged clinical record of E. T., a woman, aged 20. This patient gave a positive blood culture on April 11 following a mastoidectomy on April 6. The jugular vein was ligated on April 12. Transfusions were given on April 11 and April 14. A commercial erysipelas serum was administered on April 16 on account of a cutaneous eruption which had been recognized the day before. The blood culture remained positive on April 18 and April 26. On April 30 intravenous serum therapy was begun, a total amount of 24 cc., equivalent to 60,000 units, being administered in four days by intravenous injection. The patient was discharged in good condition on May 9.

the titer of the concentrated serum being 2,500 units per cubic centimeter. A furuncle on the left buttock, incised on May 2, yielded pus containing only Staphylococcus albus but no streptococci. A blood culture taken on May 5 remained sterile. The patient was discharged May 9, in good condition.

Case 7.—D. M., a nurse, aged 21, became ill with a sore throat on Feb. 5, 1933, and with pain in both ears on February 7. She was admitted to the hospital on February 8, on which day her temperature reached 103 F. Her abridged clinical record is shown in chart 7. After an uneventful week, on February 14 a

red and tender area appeared just below the right knee. On the next day, similar but somewhat smaller red tender areas appeared on both legs and on the hands. The eruption was diagnosed by a dermatologic consultant as erythema nodosum of infectious origin. The patient gave a history of a similar eruption four years before, with a streptococcic sore throat. On February 15, while undergoing an irrigation of the right antrum, she fainted, and two days later after treatment of her nose she went into an alarming collapse, with pale face and lips, profuse diaphoresis, a rapid and feeble pulse and apparent unconsciousness. The pupils were not dilated, and they reacted to light. She rallied quickly. On February 20 the eruption had extended above the elbows and knees. The joints were tender, and there was a purulent discharge from the nose in which abundant hemolytic streptococci were recognized on culture. A blood culture taken on February 21 was negative. On February 22 the concentrated streptococcus serum was given in divided doses to insure desensitization, the total amount on this day being 40,000 units subcutaneously. A similar amount was given the next day in two doses. The temperature reached 103.8 F. and the pulse 120 per minute at 8 p. m., two

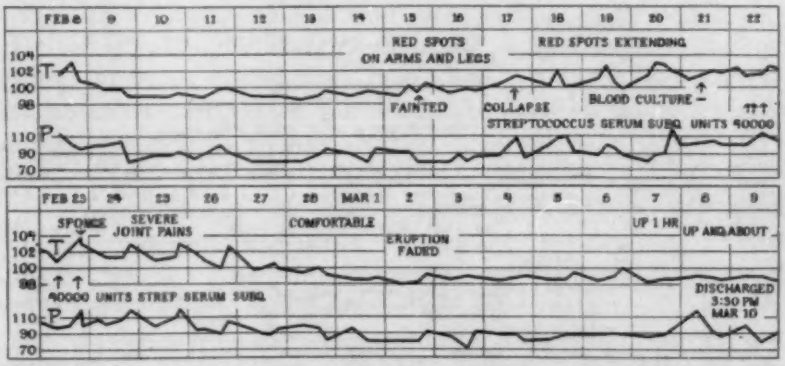

Chart 7.—Abridged clinical record of D. M., a woman, aged 21. This patient had a severe rhinitis involving the sinuses. On February 15 an eruption developed which was diagnosed as erythema nodosum. The blood culture remained negative. The patient received streptococcus serum, 40,000 units on February 22 and 40,000 units on February 23, all subcutaneously. Her recovery was satisfactory.

hours after the last injection of serum. On February 24 the joints of the hands and feet became painful. The cutaneous lesions ceased to extend but remained painful to the touch. The patient was very uncomfortable. By February 27 these manifestations had subsided, and the use of codeine was discontinued. Irrigation of the right antrum brought out a large amount of green pus. By March 5 the nasal inflammation had subsided. The patient was up and about on March 8 and was discharged on March 10. There was no late serum reaction.

CASE 8.—J. L., a man, aged 48, first presented himself in the outpatient service on Feb. 8, 1933, on account of persistent cough, pain on swallowing and the coughing of blood. Examination revealed edema over the arytenoids, especially the right, with thickening of the mucous membrane in the interarytenoid space and in the right pyriform sinus. A biopsy specimen taken on February 13 revealed a noncornifying squamous cell carcinoma. On February 23, a more thorough laryngoscopic examination under local anesthesia disclosed ulceration and general

infiltration of the laryngeal surface of the epiglottis reaching as far as the lingual surface, and extension of the new growth downward and forward to the right side of the larynx and right pyriform sinus. Examination again under anesthesia on March 13 showed carcinoma involving the larynx and the oropharynx. The laryngeal portion of the pharynx appeared not to be invaded. On April 3 the patient was admitted to the hospital for radical operation. His abridged hospital record is shown in chart 8.

On April 5 a total laryngectomy and pharyngotomy were performed. A tube was passed through the nose into the duodenum and left in place for feeding. A tracheotomy tube was inserted into the trachea. The communication between the esophagus and the trachea was filled with molded paraffin attached to the tracheotomy tube. A rubber drain was left on each side of the neck. The operation required four hours and twenty-five minutes and was finished at 5:55 p. m. Two days later the coughing increased so as to be almost continuous; there was abundant thick mucus present, and the patient appeared to become gradually exhausted. Bacteriologic study of the exudate and of the tracheal mucus taken on April 8

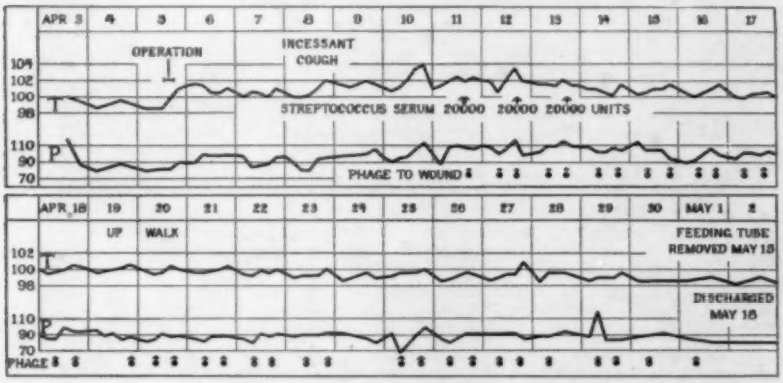

Chart 8.—Abridged clinical record of J. L., a man, aged 48, operated on for carcinoma of the larynx extending into the pharynx, on April 5. Following the operation he did badly, and the outlook appeared serious on April 11. Streptococcus serum was given on April 11, 12 and 13, and staphylococcus bacteriophage was applied to the wounds repeatedly. The patient made an excellent recovery and at the last report had remained without recurrence.

revealed chiefly hemolytic streptococci with somewhat less abundant staphylococci. On April 11, the concentrated streptococcus serum was given in divided doses, intracutaneously and subcutaneously, the total amount being 20,000 units, and on the same day application of staphylococcus bacteriophage to the surfaces of the wound was begun. The injection of the serum was repeated on April 12 and April 13, and the application of the bacteriophage was continued to May 1. The hopeless aspect of the situation changed quickly. The patient was up and about after April 19. The feeding tube was dispensed with on May 15, and the patient was discharged on May 18. He has returned periodically to the outpatient service and, according to recent reports, is leading an active life without evident recurrence of the neoplasm.

COMMENT

The eight patients selected for presentation in this paper do not represent a homogeneous group but they have one feature in common, namely, a clinical interest for the specialist in otorhinolaryngology. The presenting signs and symptoms caused the patients to be assigned to the otorhinolaryngologic services. Of the eight patients, six were allowed to reach a stage of invasion of the blood stream by hemolytic streptococci before the serum was administered. In the other two patients there was no positive blood culture. There were two deaths and six survivals.

As a rule, the serum therapy was begun by small doses, the first one being administered intracutaneously as a test for hypersensitiveness to horse serum, followed after a half an hour by a small subcutaneous dose. After this we gave the full dosage to those persons who were not hypersensitive, but proceeded with more caution in those showing an urticarial wheal at the intracutaneous site. Intravenous, intramuscular and subcutaneous routes were employed. We favor the former for prompt effect and prefer the subcutaneous route in hypersensitive patients and in cases in which the situation does not demand prompt effect.

Untoward effects which may be ascribed to the horse serum itself were observed in three patients. M. S., aged 4 years, reacted with an urticarial wheal to the initial intracutaneous injection of serum. The continuation of the serum treatment by subcutaneous and intramuscular routes was free from any other untoward manifestations. E. T., aged 20, had received an injection of erysipelas serum on April 15 and on that account was expected to be hypersensitive to horse serum on April 30, when the concentrated serum was used. Actually, the initial intracutaneous injection at this time did disclose a marked hypersensitiveness. However, because of the desperate state of the patient, the second injection of 1 cc. was given intravenously after an interval of thirty minutes and a third intravenous injection of 3 cc. three hours later. Following this there was a chill lasting thirty minutes and a rise in temperature to 102.6 F. However, the subsequent intravenous injections of 5 cc. each were without evident reaction, and there was no late cutaneous rash. D. M., aged 21, appeared not to be hypersensitive on intracutaneous injection of the serum on February 22. However, she suffered pains in her joints on February 24 and 25, which may have been caused by the serum. There was no late cutaneous rash. In this series, therefore, the serum reactions did not cause any grave disturbances.

The two fatalities deserve special consideration. Both patients were young children. S. W., aged 4 months, was the victim of an infection of the upper respiratory tract, otitis media and mastoiditis. After a

positive blood culture taken on the tenth day of the illness a single intramuscular injection of 10,000 units of the concentrated serum was given on the following day. A day later the left mastoid was opened and the left jugular vein ligated. Another dose of 12,000 units of serum was given on March 23, the sixth postoperative day. Autopsy disclosed advanced destruction of the right mastoid with a dissecting abscess extending from it to the mediastinum. The second fatality occurred in a boy, M. C., aged 4½ years, who had been subjected to repeated instrumental esophageal dilations for congenital stricture. In this case we were confronted with an acute vegetative endocarditis due to the hemolytic streptococcus, apparently a sequel of a chronic inflammation in the mediastinum about the malformed and ulcerated esophagus. In both of these patients the serum treatment was a failure. What might have been accomplished by earlier adequate doses of the serum is a matter for conjecture.

Two of the patients survived with persistent disease of the bone. In one of them, A. G., 11 months of age, destructive arthritis and epiphysitis developed at the right hip early in April, almost two months before the positive blood culture was first obtained. The serum was administered subsequent to the positive blood culture. The other one, M. S., aged 4 years, received 100,000 units of the serum from May 12 to 16 after a positive blood culture taken on May 9. Almost two weeks after the last injection of serum the blood culture still revealed 3 colonies per cubic centimeter of blood, and a month after the last dose osteomyelitis of the left femur became manifest. The experience with these two patients led us not only to favor early administration of the serum in adequate dosage but also to continue the injections in smaller amounts over several weeks in the streptococcic infections of the blood stream in children in order, if possible, to afford protection to the skeleton as well as to other important structures.

The remaining two patients with septicemia recovered without serious sequelae. F. C., aged 6 years, recovered so promptly following 40,000 units of the concentrated serum and one transfusion that one would be skeptical about the diagnosis of bacteremia were it not for the two positive blood cultures. The other patient, E. T., aged 20, had a prolonged sepsis which appeared to have been ameliorated by the commercial streptococcus serum given for the erysipelas on April 16. However, the bacteremia persisted until, as a measure of desperation, the concentrated serum was given intravenously, with a dramatically favorable result. This patient was ill in 1932, when our experience with this serum was still limited.

Of the eight patients, the two oldest, D. M. and J. L., escaped without recognized bacteremia. D. M., a nurse, aged 21, was ill enough

for consultation in which the bacteriologists were included, and the suggestion to employ serum was accepted. The subsequent course of the illness was highly gratifying, but the part played by the serum may be questioned. We think that it helped considerably. J. L., aged 48, subjected to an extensive mutilating operation for radical removal of a laryngeal carcinoma already extrinsic, suffered the usually unavoidable infection of the operative site with the pharyngeal bacteria. An apparently desperate condition was promptly relieved during the use of the concentrated streptococcus serum in combination with local application of staphylococcus bacteriophage to the wound, and we are inclined to the belief that these agents contributed an essential part to this relief, an opinion also shared by the surgeons in the case.

The records of the eight patients here discussed offer strong evidence in favor of the use of streptococcus serum, particularly the concentrated streptococcus serum of the New York State Department of Health, in the treatment of streptococcic infections of the respiratory tract, ear and mastoid, as well as the infections of the blood stream developing as sequelae to these. We hope to persuade our clinical friends in this field to employ the serum earlier and in adequate dosage so as to forestall these more dangerous sequelae rather than to await a desperate or well-nigh hopeless situation before considering serum therapy. Early bacteriologic examination leading to a prompt recognition of the infecting organisms is the obvious key to this type of therapy.

SUMMARY

1. Eight patients suffering from severe infection with hemolytic streptococci in the field of otorhinolaryngology, six of them with positive blood cultures, were treated with the concentrated streptococcus serum of the New York State Department of Health, with two deaths and six recoveries.

2. The early use of this serum is indicated in streptococcic infections of the upper respiratory tract and the middle ears in order to forestall the all too common serious sequelae of these maladies.

3. Postoperative infections in the upper respiratory tract may also be favorably influenced by this serum.

RELATIONSHIP OF INFECTION TO POSTOPERATIVE PULMONARY COMPLICATIONS

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Recent studies of postoperative pulmonary complications have indicated that bronchopneumonia, bronchitis and collapse of portions of the lung show the highest incidence.[1] These three complications may logically be considered together since they occur together postoperatively and have long been observed by pathologists in the same lungs.[2] It seems possible that they have certain etiologic factors in common.

A thorough study of such etiologic factors as infection, diminished ventilation of the lungs and bronchial obstruction has shown that no single one adequately explains the development of pulmonary complications. Infection by pneumococci occurs regularly in postoperative bronchopneumonia,[3] but the invasiveness of the organisms is of such low degree that their entrance into the lungs and their proliferation are probably aided by other conditions. Although diminution in the venti-

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From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), and the Fifth Surgical Service (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

1. King, Donald S.: Postoperative Pulmonary Complications: I. A Statistical Study Based on Two Years' Personal Observation, Surg., Gynec. & Obst. **56**:43, 1933. Fuller, C. J.: Analysis of Pulmonary Complications Based upon Cases at the University College Hospital, London, in One Year, Lancet **1**:115 (Jan. 18) 1930.

2. Gairdner, W. T.: On the Pathologic States of the Lung Connected with Bronchitis and Bronchial Obstruction, Month. J. M. Sc. **11**:122 and 230, 1850; **12**:440, 1851; **13**:2 and 238, 1851.

3. (*a*) Whipple, A. O.: A Study of Post-Operative Pneumonitis, Surg., Gynec. & Obst. **26**:29, 1918. (*b*) Cleveland, M.: Further Studies in Post-Operative Pneumonitis, ibid. **28**:282, 1919. (*c*) Gundel, M.: Bakteriologische Untersuchungen an Leichenlungen unter besonder Berücksichtigung ihrer Bedeutung für das Pneumonie Problem, Ztschr. f. Hyg. u. Infektionskr. **112**:623, 1931.

lation of the whole lung is an important predisposing cause, it is not more marked in cases in which complications develop than in those in which no complications occur.[4] Collapse of the lungs is primarily the result of bronchial obstruction.[5] Yet obstruction by a mucous plug of any passage smaller than a primary bronchus is ineffective unless there is simultaneous interference with collateral respiration between alveoli.[6] It is also true that both the production and the subsequent injurious effects of mucous plugs are largely conditioned by the presence of infectious agents. Conclusive evidence that collapse is the usual precursor of bronchopneumonia has not been obtained. It seems more than likely that the complications to be considered are not due to a single cause but to the interaction of two or more causative factors. In this study particular attention has been devoted to the interrelationships of infection and diminished ventilation.

A series of patients among whom a high incidence of the more common postoperative pulmonary complications might be expected to occur were observed. Pulmonary changes of slight degree, as well as clearly defined complications, were noted by physical and roentgenologic examinations. In the same patients a systematic study of the well known pathogenic bacteria of the nasopharynx was undertaken.

PULMONARY CHANGES FOLLOWING OPERATION

Procedure.—Sixteen patients about to undergo operations on the upper part of the abdomen were selected for observation, as about 10 per cent of such patients have definite postoperative pulmonary complications.[1] The preliminary period of observation in the hospital which

4. (*a*) Muller, G. P.; Overholt, R. H., and Pendergrass, E. P.: Post-Operative Pulmonary Hypoventilation, Arch. Surg. **19**:1322 (Dec., pt. 2) 1929. (*b*) Powers, John H.: Vital Capacity: Its Significance in Relation to Post-Operative Pulmonary Complications, ibid. **17**:304 (Aug.) 1928. (*c*) Churchill, E. D., and McNeill, D.: The Reduction in Vital Capacity Following Operation, Surg., Gynec. & Obst. **44**:483, 1927. (*d*) Beecher, Henry K.: The Measured Effect of Laparotomy on the Respiration, J. Clin. Investigation **12**:639 (July) 1933. (*e*) Carlson, Herbert A.: Inhibition of Respiration as a Factor in the Pathogenesis of Post-Operative Pulmonary Complications, J. Thoracic Surg. **2**:196, 1932. (*f*) Allen, K. D. A.: Post-Operative Behaviour of the Diaphragm, Radiology **16**:492 (April) 1931. (*g*) Breuer, F.: Ueber einseitige postoperative Zwerchfellschaedigung, Arch. f. klin. Chir. **161**:443, 1930. (*h*) Klotz, L., and Straaten, T.: Postoperative Hypoventilation der Lungen, Klin. Wchnschr. **10**:1952 (Oct. 17) 1931.

5. Elliott, T. R., and Dingley, L. A.: Massive Collapse of Lungs After Surgical Operations, Lancet **1**:1305, 1914. Coryllos, P. N., and Birnbaum, G. L.: Obstructive Massive Atelectasis of the Lung, Arch. Surg. **16**:501 (Feb.) 1928.

6. Van Allen, C. M., and Lindskog, G. E.: Obstructive Pulmonary Atelectasis: Problems of Pathogenesis and Clinical Management, Arch. Surg. **21**:1195 (Dec.) 1930.

is common in conditions involving the upper part of the abdomen allowed time for an adequate preoperative examination. A history was taken, with particular attention to respiratory and cardiac illnesses and to colds, sinusitis and dental or gingival infections. The physical examination was made with especial attention to the thorax and thoracic organs. Roentgenograms were made with the patient in bed in a position similar to that to be assumed after operation.[7] The technic was such [8] that the tube-plate distance, the length of exposure and the direction of the rays were standardized and thus allowed comparison of successive roentgenograms. The physical and roentgenographic examinations were repeated every two to four days after operation for a period of two weeks, or until no further changes were noted.

Symptoms and Physical Findings.—The clinical data for the whole group of patients are summarized in table 1. Except for one appendectomy the operations were performed on the upper part of the abdomen. The anesthetic employed was ether alone or ether preceded by nitrous oxide and oxygen, with the exception of one case in which avertin was administered rectally. Unless otherwise stated all the abnormal symptoms and physical signs appeared within four days after the operation. Most of the symptoms were observed on the second or third postoperative day.

Symptoms referable to respiratory disease were usually of slight degree, such as cough, sputum, fever or a feeling of "catching cold."

In six patients cough developed; in four the cough was productive. A postoperative rise in temperature, for which the operation itself may have been partly responsible, was present in all and varied considerably in duration. It is noteworthy that in five instances the patient described the subjective symptoms during his postoperative course as similar to those accompanying "catching cold." This did not refer to the characteristic symptoms of coryza, which could not be found on examination of the nose and pharynx, but probably had to do with irritation of the nose and throat and with general malaise. Striking symptoms usually associated with pneumonia were rare. Pain in the chest was noted in only one case eight days after operation and gave rise to the diagnosis in infarction of the lung. Cyanosis was present in one severe case of bronchopneumonia. Chills did not occur in any case.

In contrast to symptoms, physical signs of pulmonary changes were present in all the patients in varying combinations and in varying degree. They ranged from an elevation of the diaphragm with corresponding physical signs to signs of a well marked collapse of a lobe or of a well

7. A portable roentgenographic apparatus was used for this purpose by one of us (B. F. S.) through the courtesy of Dr. P. F. Butler, radiologist to the Boston City Hospital.

8. Steele, Brandt F.: To be published.

defined bronchopneumonia. Elevation of the diaphragm was the most constant change, appearing postoperatively in all the patients. It was best recognized and measured in roentgenograms. It gave rise to dulness and scattered transient râles at the bases of the lungs posteriorly. In addition to signs readily ascribed to the elevated position of the diaphragm, other signs of pulmonary changes were frequently present. Râles were found in nine cases, dulness in six, diminished breath sounds in four and bronchial breathing in six. Patchy roentgenographic shadows appeared postoperatively in six cases and diffuse haziness of the lung in three. A similar high incidence of physical signs of pulmonary and diaphragmatic changes has been noted by other observers following operations on the upper part of the abdomen.[9]

Diagnosis.—A diagnosis of the thoracic condition was readily made in certain cases (table 1). In four cases nothing more than an elevation of the diaphragm with corresponding physical signs was observed (cases 1, 2, 3 and 13). These patients were said to have "hypoventilation," after the suggestion of Muller, Overholt and Pendergrass.[4a] They represent the group with the minimum of postoperative pulmonary changes observed in the whole series of sixteen patients. In two other cases outspoken symptoms and signs of pulmonary complications were noted: lobar collapse in case 7 and bronchopneumonia in case 10. These two cases represent the maximum of postoperative changes observed. It is possible that only cases of maximum severity, such as the latter two, have been noted by observers who have determined the incidence of postoperative pulmonary complications. Two cases out of a total of sixteen represent only a slightly greater frequency than the 10 per cent quoted as the usual incidence. Owing to close observation in the present series, however, definite roentgenologic evidence and physical signs of less severe respiratory complications were found in nine other patients. Two of them had a mild bronchitis, one had a collapse, two had a combination of collapse and bronchopneumonia and one had a combination of infarction and bronchopneumonia. The diagnosis was more difficult in four of the cases. Three of these were finally called bronchopneumonia because of the physical findings listed in table 1 (cases 12, 14 and 15). Thus the incidence of postoperative pulmonary complications was eleven out of sixteen, or 69 per cent.

The fourth patient (case 16), who showed a persistent fever, elevation and fixation of the right half of the diaphragm and obliteration of the right costophrenic sinus, probably had subphrenic peritonitis due to escape of bile or other material at operation.

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9. Overholt, Richard H., and Veal, J. Ross: The Incidence, Character and Significance of Abnormal Physical Signs in the Chest Occurring After Major Surgical Operations, New England J. Med. **208**:242 (Feb. 2) 1933.

TABLE 1.—*Summary of Clinical Data*

Patient	Operation	Anesthesia	Symptoms	Physical Signs	Roentgenographic Findings: Lungs	Diaphragm Elevation, Cm.: Right	Diaphragm Elevation, Cm.: Left	Diagnosis	Comment
1 J. T.	Cholecystotomy	Nitrous oxide and oxygen, ether	Fever (3 days)	Diminished breath sounds and few scattered râles at bases	Clear	2.5	1.0	Hypoventilation	
2 H. M.	Cholecystectomy	Nitrous oxide and oxygen, ether	Fever (5 days)	Few transient scattered râles at bases	Clear	2.0	2.0	Hypoventilation	Frequent colds; sore throat
3 M. D.	Colostomy	Ether	Fever (5 days)	Diminished breath sounds at bases	Clear	5.0	3.0	Hypoventilation	
4 E. F.	Exploratory laparotomy	Nitrous oxide and oxygen, ether	Fever (10 days); cough; caught cold	Scattered râles throughout lungs	Clear	6.0	3.0	Bronchitis	
5 M. McL.	Cholecystogastrostomy	Ether	Fever (10 days); caught cold; cough; sputum	Scattered râles throughout lungs	Clear	6.0	3.0	Bronchitis	
6 M. Di R.	Cholecystotomy	Nitrous oxide and oxygen, ether	Fever (3 days)	Left side of thorax decreased in size; left side of thorax, dulness, diminished breath sounds	Left side of chest diffusely clouded; mediastinum slightly to left	7.0	6.0	Collapse of left lung	
7 T. J.	Cholecystostomy	Nitrous oxide and oxygen, ether	Fever (5 days); asthmatic dyspnea	Dulness, diminished breath sounds in right lung, coarse râles and wheezes	Shadow in lower lobe of right lung; mediastinum to right	6.0	4.0	Collapse of right lung	Chronic bronchitis and bronchiectasis; asthma 2½ years; peptic ulcer
8 M. C.	Colostomy	Nitrous oxide and oxygen, ether	Fever (15 days); cough and sputum increased	Dulness, râles, bronchial breath and voice sounds, right side of chest posteriorly	Diffuse mottled areas and patchy shadows	2.0	4.0 (depressed)	Collapse of right lung, bronchopneumonia	Chronic bronchitis, increased 3 mos.; died 15 days after operation; autopsy showed resolving bronchopneumonia, carcinomatosis of lungs, carcinoma of splenic flexure, beta hemolytic streptococcic septicemia

9 C. P.	Exploratory laparotomy	Nitrous oxide and oxygen, ether	Fever (22 days); pain in right costal margin	Dulness, diminished and bronchial breath sounds, bases of right and left lung	Patchy shadows in lower part of chest, right and left	8.0	6.0	Infarction, bronchopneumonia	Cold 2 weeks before operation; none in hospital; carcinoma of stomach with metastases
10 P. V.	Cholecystectomy	Ether	Fever (5 days)	Bronchial voice and breath sounds; showers of fine crackling râles, both bases, more in right lung	Patchy shadows in lower part of chest, right and left	6.0	?	Bronchopneumonia	Chronic bronchitis 15 years; died 6 days after operation; no autopsy
11 A. B.	Partial gastrectomy	Avertin, nitrous oxide and ether	Fever (4 days); caught cold; cough; sputum	Dulness, bronchial breath sounds, medium moist râles posteriorly in right side of chest	Patchy shadows, diffuse shadow in right side of chest	5.0	5.0	Collapse of right lung; bronchopneumonia right lung	Frequent colds
12 N. F.	Cholecystectomy	Nitrous oxide and oxygen, ether	Fever (9 days)	Dulness, increased voice sounds, showers of fine râles at base of right lung near spine	Small shadow in lower part of chest, right	6.0	4.0	Bronchopneumonia	Slight cough for 1 week before operation
13 E. P.	Cholecystectomy	Ether	Fever (12 days); caught cold	Diminished breath and voice sounds in right side of chest	Clear; thoracic scoliosis to right	3.0	?	Hypoventilation	Clinical course suggested pulmonary complication
14 R. S.	Appendectomy	Ether	Fever (5 days); caught sold	Bronchial breath sounds and râles at base of right lung	Clear	2.0	2.0	Bronchopneumonia	Frequent colds for 5 mos. before operation; last 3 days before operation
15 A. H.	Cholecystectomy	Ether	Fever (4 days); slight cough; sputum	Bronchial breath sounds and râles in showers at base of right lung posteriorly	Clear	7.0	4.0	Bronchopneumonia	Chronic sinusitis; pyorrhea
16 F. W.	Cholecystectomy; repair of common duct	Ether	Fever (28 days)	None	Lung clear; right side of diaphragm high, fixed; costophrenic sinus obliterated	10.0	6.0	Subphrenic abscess, bile ? foreign body ?	Chronic cough and sinusitis 15 years; purpura postoperatively

REPORT OF CASES

The following report of cases gives the complete description of four cases in which pulmonary findings were characteristic and relatively unmodified by unrelated conditions.

CASE 10.—*History.*—P. V., a man, aged 46, entered the hospital complaining of intermittent pain in the right upper abdominal quadrant and vomiting. He had had a chronic productive cough for thirteen years. Physical examination revealed dental caries, oral sepsis, slight inflammation of the pharynx and numerous fine moist râles in the bases of the lungs posteriorly. Roentgenograms showed prominent trunk markings toward the bases but were otherwise negative.

A diagnosis of cholecystitis was made. Cholecystectomy was performed under ether anesthesia, lasting one and a half hours. Induction of anesthesia was difficult owing to marked excitement. The patient's respirations were irregular, and he was slightly cyanotic.

Postoperative Course.—On the first postoperative day the temperature rose to 101.4 F., and the pulse rate was 136. The patient was unable to cough because of pain in the wound. Moderate distention was present. The breath sounds were loud and harsh anteriorly and in the right side of the chest posteriorly. A roentgenogram showed patchy shadows at the bases of both lungs. The diaphragm was elevated 6 cm. on the right and 5 cm. on the left. On the second day the distention was more severe. Bronchial voice and breath sounds were heard at the bases of both lungs, and medium-sized and fine moist râles were heard throughout the chest. By the fourth day the respiratory rate had risen to 40. The physical signs remained the same. The cough was productive of a thick purulent sputum. Roentgenograms showed extensive patchy shadows at the bases of both lungs. On the fifth day the temperature was 101.6 F., the pulse rate 130 and the respiratory rate 40. Breathing was labored and grunting, and distention was marked. Cyanosis appeared. Dulness, râles and bronchial breath sounds were present at the bases of both lungs. On the evening of the fifth day the temperature, pulse rate and respiratory rate rose rapidly, and the patient died. Permission for autopsy was not obtained.

Bacteriologic Observations.—A pneumococcus of type XVII was cultured from the pharynx before operation and again on the third day postoperatively. On the fourth day pneumococci of type III were cultured in large numbers from the sputum and pharynx. Blood cultures on the fourth and fifth days were negative.

Comment.—In this patient severe bilateral bronchopneumonia developed on the third day after operation and led to death on the fifth day after operation. Chronic bronchitis and oral sepsis were probably significant predisposing factors. The progress of the surgical condition was also stormy. The type III pneumococcus first appeared and predominated in the sputum and pharynx coincidentally with the appearance of pneumonia.

CASE 11.—*History.*—A. B., a white widow, aged 66, entered the hospital complaining of chronic gastric distress. A diagnosis of operable carcinoma of the stomach was made. The patient was subject to frequent slight colds and had had one attack of bronchitis three years before admission. Physical examination showed that the lungs were clear and the mouth and throat normal.

A partial gastrectomy was performed under rectal administration of avertin as a basic anesthesia, with nitrous oxide and oxygen for one hour and a small amount of ether for ten minutes. The operation lasted two hours and fifteen minutes.

Postoperative Course.—The patient felt quite comfortable for the first two postoperative days. The right half of the diaphragm was elevated 5.5 cm., the left 4 cm.; both sides were mobile. A few scattered râles were heard at the bases of both lungs posteriorly. On the third day the patient felt as though she had "caught cold," and coughed up thick, glairy, grayish sputum. The temperature, which had dropped to near normal, rose to 103.8 F. and the pulse rate to 120. The breath sounds were harsh, and a few râles were heard in the bases posteriorly. On the fourth day the physical signs were the same, but a roentgenogram showed patchy shadows in the bases of both lungs and a diffuse clouding of the entire right side of the chest. The temperature and pulse rate returned to normal. On the following day, in addition to the râles, dulness and harsh breath sounds with a bronchial quality were noted at the base of the right lung posteriorly. The cough, sputum, physical signs and roentgenographic shadows gradually disappeared, and the patient had recovered from the pulmonary complication by the tenth postoperative day. She was discharged on the twenty-second postoperative day with the surgical condition improved.

Bacteriologic Observations.—No respiratory pathogens were cultured from the pharynx before operation or on the first postoperative day. A pneumococcus of type XXXI was cultured from both the pharyngeal swab and sputum on the third day, from the sputum on the fourth day and from the pharynx on the twelfth and fifteenth days. No pneumococci were found on the seventh and eighteenth days or on two occasions six weeks and five months after operation.

Comment.—The respiratory symptoms of postoperative pulmonary collapse and bronchopneumonia were remarkably slight, and the physical signs were much less than might have been expected from observation of the roentgenograms. A pneumococcus appeared in the sputum and pharynx coincidentally with the postoperative pulmonary complication.

Case 6.—*History.*—M. Di R., an Italian woman, aged 37, was admitted with a story of severe abdominal pain, nausea, vomiting, poor appetite and jaundice for one month. Moderate tenderness and voluntary spasm were found in the right upper quadrant of the abdomen.

Physical Examination.—The patient was moderately obese and did not appear acutely ill. Her incisor and canine teeth were quite carious, and pyorrhea was marked. The examination of the chest showed no abnormal findings.

Operation.—Cholecystectomy was performed, revealing acute subsiding cholecystitis and cholelithiasis. A transduodenal incision into the ampulla of Vater was made for removal of a large irregular stone. Nitrous oxide and oxygen were used for the induction of anesthesia and were followed by ether, of which 11 ounces (342.14 Gm.) was used. The anesthesia lasted forty minutes, and the operation thirty-three minutes. The course of the anesthesia and operation was uneventful.

Postoperative Course.—On the first day after operation the patient complained of abdominal pain; the temperature rose to 102 F. and the pulse rate to 120. Roentgenograms showed diffuse clouding of the left side of the chest with narrowing of the left intercostal spaces and bilateral elevation of the diaphragm. On the second day a relatively smaller size and decrease in the breath sounds in the left side of the chest were noted. On the third postoperative day the mediastinum was seen at the left of the midline in a roentgenogram taken at the height of inspiration. Gastro-intestinal complaints were not present after the third day. The temperature and pulse rate decreased gradually and were normal on the twelfth postoperative day, and the physical signs and roentgenologic changes dis-

appeared at about the same time. The patient was discharged from the hospital on the seventeenth day after operation.

Bacteriologic Observations.—A pneumococcus of type XIV was found in one of two preoperative and in five of six postoperative specimens.

Comment.—The diagnosis of collapse of the left lung was obvious in this case, and there was apparently no bronchopneumonia. The postoperative course, with the exception of the physical findings, was not such as to arouse suspicion of a pulmonary complication. A pneumococcus of type XIV was persistently present in the pharynx.

CASE 3.—*History.*—M. D., an Irish housewife, aged 52, was admitted to the hospital on Feb. 15, 1933, complaining of abdominal cramps and pain for two months accompanied on one occasion by a shaking chill.

In the past the patient had had frequent colds with sore throats and hoarseness. These ceased two years before admission. During the present illness of two months the hoarseness reappeared occasionally.

Physical Examination.—The tonsils were slightly large but not inflamed. The right anterior faucial pillar was quite red. No teeth other than two carious lower canines and four lower incisors were present. All these were surrounded by pyorrheic gums. The heart was moderately enlarged, the apex being 12 cm. to the left in the fifth space. A soft blowing systolic murmur was present at the apex.

Operation.—An exploratory laparotomy and cecostomy were performed. A mass was palpated in the sigmoid colon, and multiple metastases were found in the peritoneal coats of the intestines and lymph glands. Ether was used as the anesthetic; 7 ounces (217.7 Gm.) was required during sixty minutes. During the anesthesia the pulse rate rose gradually from 80 to 120 and the respiratory rate rose to 52 in the first ten minutes, remaining about 50 until the close of the operation when it fell to 38. The operation lasted forty-five minutes. The cecostomy was performed forty-eight hours after the initial operation.

Postoperative Course.—During the first twenty-four hours after operation severe gas pains and slight distention were present; the breath sounds were fainter than normal in the right side of the chest; the temperature was 100 F. and the pulse rate 104. The results of roentgenologic examination were negative, except for marked elevation of the right side of the diaphragm and slight elevation of the left. Indigestion persisted for six days, the diminished respiration in the right side of the chest for seven days, the elevation in temperature for four days and the increase in pulse rate for one day. The diaphragm resumed its normal position on the fourteenth postoperative day. The patient was discharged on the twenty-first postoperative day unimproved.

Bacteriologic Observations.—No pneumococci were found in the sputum on three preoperative and on four postoperative examinations.

Comment.—The only noteworthy findings were the elevation of the right side of the diaphragm and the diminished breath sounds. A diagnosis of hypoventilation was made. No respiratory pathogens were found.

These four cases illustrate pulmonary complications that are relatively common after operations on the upper part of the abdomen. They range from conditions that may be considered as physiologic alterations to definite pathologic changes and include variations between

these extremes. During the progress of this work other pulmonary complications were observed in patients who were not studied before operation. These included lobar pneumonia, pulmonary abscess, encapsulated pleural effusion, collapse of a lobe of the lung with explosive onset, acute infection of the lung with organisms of the Bacillus Welchii group, pulmonary embolism and localized edema of the lung associated with carcinomatosis and phrenic exeresis. Such conditions are relatively infrequent and depend on the presence of unusual circumstances. The present report is confined to the milder changes that occur in some degree following most or all operations on the upper part of the abdomen and the most common pulmonary complications.

BACTERIOLOGIC OBSERVATIONS

Methods.—Repeated examinations of the pharyngeal flora were made, in the majority of cases on three occasions before operation and at intervals of from one to four days postoperatively. A cotton swab was passed over the nasopharynx and tonsils and placed in 5 cc. of dextrose blood broth which was shaken vigorously. The broth was cultured at once on the surface of poured blood agar plates. The broth and swab were incubated at 37 C. for two hours, and 0.5 cc. was injected into the peritoneal cavity of a white mouse. Respiratory pathogens were isolated in pure culture for identification. The serologic type of each strain of pneumococcus was determined by means of agglutinating serums specific for thirty-one types.[10]

Results of Bacteriologic Examinations.—A summary of the organisms isolated from the pharyngeal secretions and sputums in the sixteen cases studied clinically is given in table 2. The respiratory pathogens most frequently found were various types of pneumococci. Other significant organisms were the beta hemolytic streptococcus, Friedländer's bacillus (Encapsulatus pneumoniae) and a nonspecific, mouse-virulent alpha hemolytic streptococcus. Table 2 also shows the relationship between the presence of these respiratory pathogens and the occurrence of pulmonary complications.

In regard to the presence of respiratory pathogens three groups of cases may be distinguished:

1. One group (cases 1, 2 and 3) which showed no pneumococcus at any time. These patients all manifested the minimum of postoperative pulmonary changes, called hypoventilation.

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10. Cooper, G.; Edwards, M., and Rosenstein, C.: The Separation of Types Among the Pneumococci Hitherto Called Group IV and the Development of Therapeutic Subserums for These Types, J. Exper. Med. **49**:461, 1929. Cooper, G.; Rosenstein, C.; Walter, A., and Peizer, L.: Further Separation of Types Among Pneumococci Hitherto Included in Group IV and Development of Therapeutic Antisera for These Types, J. Exper. Med. **55**:531, 1932.

2. Six cases which showed a pneumococcus or beta hemolytic streptococcus constantly or intermittently, but with no relationship to a pulmonary complication. A diagnosis of pulmonary complication was made in each of these cases; bronchitis in cases 4 and 5, collapse in cases 6 and 7, collapse associated with bronchopneumonia in case 8 and infarction and bronchopneumonia in case 9.

TABLE 2.—*Summary of Bacteriologic Data*

Group	Patient	Respiratory Pathogens		Diagnosis
		Preoperatively	Postoperatively	
Cases with no respiratory pathogens in pharynx	1. J. T.....	None	None	Hypoventilation
	2. H. M.....	None	None	Hypoventilation
	3. M. D.....	None	None	Hypoventilation
Cases with respiratory pathogens in pharynx not related to postoperative course	4. E. F.....	Pneumococcus type XXI	Pneumococcus type XXI, type XIX-XXIX	Bronchitis
	5. M. McL....	Pneumococcus type III, beta hemolytic streptococcus	Pneumococcus type III, type XXI, beta hemolytic streptococcus	Bronchitis
	6. M. Di R....	Pneumococcus type XIV	Pneumococcus type XIV	Collapse of left lung
	7. T. J.....	Pneumococcus type XXVIII, type XXIII	Pneumococcus type XXIII	Collapse of right lung
	8. M. C.....	Pneumococcus type III	Pneumococcus type III	Collapse of right lung, bronchopneumonia
	9. C. P.....	Pneumococcus type XXIX, beta hemolytic streptococcus	Pneumococcus untyped, beta hemolytic streptococcus	Infarction of lung, bronchopneumonia
Cases with respiratory pathogens in pharynx related to postoperative course	10. P. V.....	Pneumococcus type XVII	Pneumococcus type XVII, type III	Bronchopneumonia
	11. A. B.....	None	Pneumococcus type XXXI	Collapse of right lung, bronchopneumonia
	12. N. F.....	None	Pneumococcus type VI, type XIV, type XVI	Bronchopneumonia
	13. E. P.....	Pneumococcus type XIII	Pneumococcus type XX	Hypoventilation
	14. R. S.....	None	Pneumococcus type XX	Bronchopneumonia
	15. A. H.....	None	Alpha hemolytic streptococcus (mouse-virulent)	Bronchopneumonia
	16. F. W.....	Bacillus mucosus-capsulatus	Pneumococcus type XIX, B. mucosus-capsulatus	Subphrenic abscess

3. A group of seven cases in which a pneumococcus or, in one instance, a mouse-virulent alpha hemolytic streptococcus was found after operation coincidentally with pulmonary changes. In two of these a second type of pneumococcus was present either before or both before and after operation, and in a third a Friedländer bacillus was present throughout the course in the hospital. In the remaining four cases the organisms that appeared postoperatively were the only respiratory pathogens found.

Bronchopneumonia was present in five cases of this group; severe pneumococcus type III pneumonia that proved fatal occurred in case 10; bronchopneumonia associated with collapse, in case 11, and quite mild bronchopneumonia, in cases 12, 14 and 15. Hypoventilation was present in case 13, and a subphrenic bile peritonitis was present in case 16.

The presence of pathogenic bacteria in the upper respiratory tract is related in several ways to the postoperative clinical course. Patients without pathogenic bacteria had hypoventilation but no other evidence of pulmonary involvement, while most patients with pathogenic bacteria had signs and symptoms of pulmonary involvement other than hypoventilation. The latter group includes one patient with severe bronchopneumonia due to type III pneumococci. The conclusion may readily be drawn that the pulmonary signs were the result of the presence of the micro-organisms, and the severity of the pulmonary lesion was proportional to the virulence of such organisms.

Other interesting aspects of the bacteriologic observations require comment. Case 5, in which the type III pneumococcus was present constantly in the pharynx may be compared with case 10 in which a fatal type III bronchopneumonia occurred. In the former the general postoperative reaction was slight, and the patient's temperament was such that he did not rest quietly in bed longer than he was forced to by the anesthetic and medications. In the latter patient abdominal pain and distention were evident after operation, with a resulting limitation of changes in position and of respiratory excursions. He also had a marked chronic bronchitis with purulent sputum. The type III pneumococcus was not found before operation but appeared after operation at the onset of definite pneumonia. The modifying influence of bronchial drainage, assisted by frequent changes in position, on the severity of postoperative complications in the presence of virulent organisms is suggested by this comparison. The preexisting infection in the bronchi and lung may have been an important deleterious influence in the case in which bronchopneumonia developed.

In tables 1 and 2 a general relationship may be observed between the presence of respiratory pathogens and chronic infection of the upper respiratory tract, and to a lesser extent between these organisms and recent acute infection of the upper respiratory tract. There is also a similar association between the presence of chronic nasopharyngeal and bronchial infection and postoperative pulmonary signs and symptoms.

Patients with collapse of portions of the lung are included among those from whom pneumococci or other pathogens were obtained. In the most severe case of collapse, case 7, a chronic bronchitis with some asthmatic manifestations was noted before operation. In this patient the connection between the chronic infection and the appearance of lobar collapse of the lung due to plugging of a bronchus is apparent.

Metastatic carcinoma of the lungs was an important complication in three cases. In case 9 the primary carcinoma was in the splenic flexure of the colon. This patient had signs of bronchopneumonia in the right side of the chest which were evident only when he lay on his left side and which disappeared when the right side of the chest was dependent. Successive roentgenograms showed first shadows at the bases of both lungs, later diffuse mottling of both pulmonary fields, and before death partial clearing of both pulmonary fields. At autopsy gross examination showed chiefly congestion of the lungs, but microscopic examination showed diffuse patches of bronchopneumonia and widely disseminated collections of tumor cells in pulmonary lymphatics. Streptococcus haemolyticus was recovered from the blood stream. In another patient, not included in this series of sixteen, who had carcinoma of the stomach, the physical signs of lobar pneumonia appeared at the base of the right lung following right phrenic exeresis and exploratory laparotomy. Autopsy showed a firm, relatively bloodless sharply localized area of edema at the base of the right lung. Microscopic examination confirmed the presence of marked edema and showed small collections of tumor cells throughout the lymphatics of both lungs. In a third patient (case 8) with carcinoma of the stomach bilateral bronchopneumonia developed after operation. He was discharged against advice on the twenty-second postoperative day with persisting pulmonary infiltration. In the two cases that came to autopsy the microscopic lymphatic pulmonary metastases may have been in part responsible for the Streptococcus haemolyticus bronchopneumonia with bizarre signs in one and for the localized edema in the other. A similar condition may have been responsible for the persisting signs in the third case. Patients operated on for carcinoma of the stomach or of the upper part of the colon must be considered as a special group in regard to the development of pulmonary complications.

If the nasopharyngeal pathogenic micro-organisms had regularly been found before operation the course of events would be much clearer. Autogenous infection probably through aspiration could be assumed. But in seven of these cases the pathogenic micro-organisms appeared in the pharynx or sputum coincidentally with the signs of pulmonary disturbance. Repeated examinations before operation by a technic designed to isolate even small numbers of relatively avirulent pneumococci insure that they were absent from the pharynx at the time or hidden in inaccessible parts of the upper respiratory tract. The number of cases in which new organisms appeared indicates that it was not a coincidental observation due to the normal shifting of pneumococcic strains. The relationship of this observation to the pathogenesis of the pulmonary complications and the source of the organisms will be discussed later.

COMMENT

The high incidence of physical signs and roentgenographic changes observed by frequent examinations of lungs and thorax in this group of sixteen cases is not surprising in view of the similar findings of Muller, Overholt and Pendergrass,[4a] and of Overholt and Veal.[9] The frequency of pulmonary changes following operations on the upper part of the abdomen has also been shown through studies on vital capacity,[11] through studies of the volume of air spaces in the position at the end of tidal expiration,[4d] through studies of the respiratory movements [4e] and through studies of the postoperative elevation of the diaphragm.[12]

The interpretation of the nature of these changes is obvious in cases in which the physical signs were clearly those of an elevated position of the diaphragm or of other limitation of respiratory movements. It was also obvious in cases that presented clearcut evidence of changes such as collapse or bronchopneumonia. In some of the cases, however, the signs were slight and transient. They might have been due to compression of the lung alone, to circulatory changes in the lungs, to excessive bronchial secretion, to aspiration of oral and pharyngeal secretions, to bronchial obstruction and collapse or to infection. It is possible that all these factors are active in varying degrees at different times. In this study the pulmonary changes have been named according to the conventional terminology, bronchitis, collapse or bronchopneumonia, implying the presence of certain of these factors. It is believed that approximate justice has thus been done to all the factors listed, with the possible exception of circulatory changes about which little information is available.

The pathogenic micro-organisms found in the pharynges and sputums of the patients in this series were those which one would expect in any group of normal persons, with the exception of the postoperative appearance of new strains. Several investigators have determined that pneumococci are found in the throats of one half of normal persons on a single examination, and as the number of examinations and the period of time over which they extend are increased, the proportion found to harbor pneumococci is also increased to nearly 100 per cent.[13] Some persons carry pneumococci persistently, others

11. Powers.[4b] Churchill and McNeill.[4c]

12. Allen.[4f] Breuer.[4g] Klotz and Straaten.[4h]

13. Dochez, A. R., and Avery, O. T.: The Occurrence of Carriers of Disease Producing Types of Pneumococcus, J. Exper. Med. **22**:105, 1915. Powell, J. P.; Atwater, R. M., and Felton, L. D.: Pneumococcus Carriers Among Four Groups of Persons Over a Period of Months, Am. J. Hyg. **6**:570 (July) 1926. Gundel, M., and Linden, H.: Die Flora der Mundhöhle Gesunder und ihre Bedeutung für die pathogenese Erkrankungen der Athmungsorgane, Zentralbl. f. Bakt. (Abt. 1) **121**:349, 1931.

only at intervals and a few very rarely.[14] More than one strain may be present at one time, and changes in the strain that is present occur frequently. Other organisms, such as beta hemolytic streptococci and Friedländer's bacillus, are less often present.

The significance of the observation of pulmonary changes and pharyngeal flora in the present series of cases after operations on the upper part of the abdomen lies in the apparent relationship between the two. Patients who had no respiratory pathogens in the pharynx had the least pulmonary changes, and those who harbored such organisms showed thoracic signs of varying degrees. A further relationship between the pharyngeal flora and the postoperative pulmonary changes consists in the simultaneous appearance of postoperative pulmonary changes and a given strain of pneumococci that was not found preoperatively. Although such relationships have not been shown in any previous studies on postoperative pulmonary complications, no data have been reported that can be interpreted as contradictory. Whipple [3a] and Cleveland,[3b] working with a similar plan, but without the advantage of ready prepared serum for many specific strains of pneumococci, found that in a few patients there developed specific antibodies for a strain of pneumococci present before and after operation, but in the greater number of their cases there developed antibodies specific for a pneumococcus present only postoperatively. Moreover, their cultural results as a whole showed a greater frequency of pneumococci in the pharynx after operation than before. In regard to the organisms present in the lesion, the observations of Whipple [3a] at autopsy in seven cases and those of Gundel [3c] by pulmonary puncture in seventeen cases and at autopsy in thirty-four cases show the frequent presence of pneumococci. Such studies indicate the importance of pneumococci in well marked postoperative pulmonary lesions. The present data indicate a similar relationship in the milder, more frequent lesions.

The appearance after operation in slightly less than half of the cases of strains of pneumococci that were not present before operation brings up the question of their source. It is, of course, possible that they were present in the pharynx before operation, but in such small numbers or hidden so deeply in foci of infection that they were not found by the methods used. They may then have been mobilized by the secretions under narcotics or anesthesia, or they may have found conditions especially suitable for their proliferation. As alternative sources may be mentioned: (1) contact infection in the wards, and (2) mutation from rudimentary or rough forms of the same organism.

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14. Webster, L. T., and Hughes, T. P.: Incidence and Spread of Pneumococci in Nasal Passages and Throats of Healthy Persons, J. Exper. Med. **52**:535 (April) 1931.

From these observations it is apparent that infection by organisms common in the nose and throat is of importance in postoperative pulmonary complications. Changes in the physiology of respiration and circulation following operation are probably related to bronchitis, bronchopneumonia and collapse to the degree that they favor the penetration of micro-organisms in the lower respiratory tract and interfere with their subsequent disposal. An understanding of such relationships is necessary for the development of prophylaxis and therapy based on physiologic procedures. Measures directed against the invading micro-organism may also be considered. The study of the respiratory flora, its virulence and the immune reactions of the patient may point out certain patients who are particularly liable to severe infections. In certain circumstances, the use of immunizing methods based on procedures such as those developed by Felton [15] and Ross [16] may be of value.

SUMMARY AND CONCLUSIONS

Sixteen cases were studied before and after abdominal operations with regard to the development of postoperative pulmonary complications and to the presence of respiratory pathogens in the pharynx and sputum. A high incidence (69 per cent) of pulmonary complications was found. Three patients without pathogenic organisms in the pharynx before or after operation had the least changes in the lungs. Of the remaining thirteen patients with pathogenic organisms in the pharynx, eleven had postoperative pulmonary changes greater than the minimum. In seven cases a strain of pneumococci not recovered before operation appeared postoperatively as part of the postoperative reaction.

The presence of relationships between postoperative pulmonary complications and the pharyngeal flora indicates an avenue of approach to the study of such complications that holds promise for the development of practical prophylactic methods.

Mrs. Mildred Barnes gave technical assistance in this investigation.

15. Felton, L. D.; Sutliff, W. D., and Steele, B. F.: Antigenic Characteristics in Man of Certain Products of the Pneumococcus: Comparison with Vaccine, J. Infect. Dis., to be published.

16. Ross, V.: Oral Immunization Against the Pneumococcus, J. Exper. Med. **51**:585 (April) 1930.

SENILE OSTEOMALACIA

REPORT OF A CASE

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Porosity of bone is a frequent sequel in many pathologic states. It may be found in a single bone or in many bones in the same patient. It is, however, seldom a primary lesion causing local pain and deformity. The etiology of atrophy of bone is usually apparent, and can be classified readily under one of the following headings: (1) disuse, (2) neurogenic, (3) endocrinologic or (4) nutritional. The case reported here is unusual because: 1. The atrophy of bone was limited to the spinal column and pelvis. 2. The etiology was obscure. 3. The softening of the vertebral bodies resulted in a painful posterior curvature of the spine. 4. Rest on a convex frame yielded complete relief.

REPORT OF A CASE

Mrs. Rose Y., 65 years old, was admitted to my service at the Israel Zion Hospital, Brooklyn, because of increasing pain and deformity of her back. She had been under observation in the dispensary for about two years. During this period the backache, which was not preceded by a known injury or illness, but began insidiously, continually increased in severity. At the same time her back became kyphotic and her height noticeably diminished. The symptoms finally reached a point at which the patient was practically totally incapacitated. The pain was in the lower dorsal region, and radiated to the left side of the abdomen.

Examination revealed an elderly, fairly well nourished woman, who stood and walked without assistance. She presented kyphosis of the spine, most marked at the dorsolumbar junction. There were flattening of the chest, prominence of the lower portion of the abdomen and a horizontal crease across the upper part of the abdomen indicative of fixed flexion of the spine. The movements of the spine were markedly restricted, and there was spasm in all the muscles of the back. Pressure over the spine, especially between the eighth dorsal and the second lumbar vertebrae elicited marked tenderness. There were periarticular thickening in the fingers and moderate limitation of the motions of the shoulders. The physical examination revealed no other abnormalities.

Roentgenograms showed extensive pathologic change in the vertebrae and pelvis, but none in the skull or extremities.

The most conspicuous change was severe atrophy of the vertebrae (fig. 1), most marked in the dorsal region, with deformity of certain of the dorsal bodies. There was a short curvature to the left at the dorsolumbar junction and to the right in the midlumbar and lower lumbar areas. There was wedging of the vertebrae involved in the curvatures. The seventh, ninth and eleventh dorsal vertebrae were markedly reduced in their vertical diameters. The first lumbar

vertebra was misshapen. The outlines of all the vertebrae, except those at the dorsolumbar junction, were clearly visible, but there was marked thinning of the cortical and cancellous bone. The intervertebral disks on both sides of the seventh and ninth dorsal vertebrae were increased in size and were biconvex. Between the tenth dorsal and the second lumbar vertebrae the disks were reduced in size

Fig. 1.—The general atrophy of all the vertebrae is notable. There are a slight compound lateral curvature, a marked reduction in the vertical diameter of the seventh and ninth dorsal vertebral bodies and a marked wedge deformity of the eleventh dorsal vertebra, with apparently complete disappearance of the intervertebral space between the eleventh dorsal and the first lumbar vertebrae.

and barely distinguishable. The lumbar articulations were clearly seen. There was no peripheral lipping.

The lateral view of the spine (fig. 2) showed the lesion most marked in the dorsal section, the lumbar vertebrae exhibiting practically normal conformation.

The seventh dorsal vertebra was compressed so that its vertical diameter was scarcely more than a fourth of normal size. The greatest compression was through the center. The borders of the body were distinct, but thin; the upper border was mildly concave, the lower border markedly so. The cancellous tissue was rarefied. The posterior arch and the spinous process had a denser consistency. The ninth

Fig. 2.—The osteoporosis is very evident, particularly as it affects the dorsal spine. Note the marked reduction in the vertical diameter of the seventh and ninth dorsal vertebrae and the biconvex character of the adjacent intervertebral disks. The eleventh dorsal vertebra is wedge-shaped, with almost complete disappearance of the anterior part of the body. The tenth and twelfth dorsal vertebrae are elongated in their anteroposterior diameters.

dorsal vertebra showed the same alteration in outline, size and density as the seventh dorsal. The eleventh dorsal showed a much more advanced lesion. The body was wedge-shaped, with the base posteriorly, and of about half the normal

height, with the apex in front, the anterior half of the body being reduced to a narrow amorphous mass. It appeared to be fused with the tenth dorsal vertebra. The texture of the bone was denser than that of the adjacent vertebrae. The tenth and twelfth dorsal vertebrae appeared to be elongated in their anteroposterior diameters, which were twice the length of the vertical diameters. The anterior borders of the bones were irregular. The sixth and eight dorsal vertebrae were smaller than normal and greatly atrophied.

In the pelvis was extensive irregular rarefaction of the ischium and pubic bones on both sides, but without deformity.

The urine and blood were normal except for lymphocytosis. The blood calcium and phosphorus values were normal, and the test of the basal metabolism rate yielded a normal figure.

COMMENT

The most difficult problem in this case related to the etiology of the atrophy. A malignant process was evidently not responsible for the osseous changes, for (1) there was no primary focus anywhere in the body, (2) the lesion in the spine had existed for two years without impairment of the general health and without cachexia, and (3) the pain in the back was not as intense or as unyielding as that customarily experienced in a metastatic malignant process in the vertebrae. Hodgkin's disease was excluded by the blood cell picture. The normal values for blood calcium and phosphorus eliminated the possibility of tumor or disease of the parathyroid bodies, and the normal basal metabolic rate precluded dysfunction of the thyroid gland as a cause of the osseous pathologic process.

The clinical examination revealed no neurologic disturbances in the cerebrospinal system which could induce atrophy of bone.

Disuse as a basis for the osteoporosis may be dismissed from consideration, because the patient, despite the pain, was able to get about considerably, walking and working every day.

Thus, by a process of exclusion, my colleagues and I were compelled to conclude that the disease of the spine was nutritional or metabolic. The demineralization progressed to such a degree that it caused a partial collapse of certain of the dorsal vertebrae, with resultant pain and deformity. The nutritional upset may be considered a senescent degenerative change. Why the metabolic upheaval should appear and involve a limited portion of the skeleton is inexplicable.

TREATMENT

Though the etiology was obscure, the course of treatment that of necessity had to be pursued was readily apparent. The patient was put to bed on a canvas frame. Gradually, the frame was bent into a convex curve. This form of treatment immediately provided rest to the spine and freedom from the bearing of weight. As the curve of the frame

was increased the kyphosis of the spine was somewhat reduced. In addition, several times a day the patient received sedative doses of baking and massage of the back. The therapy was rapidly and surprisingly effective. Within three weeks the pain and tenderness disappeared, the kyphosis was reduced, and the patient, with the support of a light plaster of paris jacket, was able to move about comfortably and was discharged.

PREOPERATIVE IRRADIATION OF MASSIVE TUMORS OF THE KIDNEY

A CLINICAL AND PATHOLOGIC STUDY

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The object of this communication is to suggest for consideration a therapeutic measure which I have found helpful in facilitating the removal of large malignant tumors of the kidney. I refer to the use of preoperative high voltage roentgen therapy for the purpose of reducing the size of these enormous neoplasms. Although I feel sure that this adjunct of therapy is being introduced in some clinics, the literature as yet contains no specific report of it.

I cannot present a large series of cases, as, fortunately, a big renal tumor is not common. Also the effect that preoperative irradiation has on the chance of ultimate cure cannot be reported as this can be determined only with the passing of years. I shall, however, show the direct effect that irradiation has on the cytology and gross characteristics of these tumors and call attention to the immediate benefit of this treatment in making these tumors operable.

PRESENT STATUS OF THE OPERATIVE PROCEDURE IN RENAL TUMORS

The treatment of renal tumors has always been unsatisfactory. Considering malignant renal growths of all types and sizes, Judd and Hand [1] reported in 1929 that not more than 10 per cent of their patients had lived as long as ten years after nephrectomy and that few had survived three. In children the prospect is even more unfavorable, as about 90 per cent die within a year after operation (Hyman,[2] Kretschmer and Hibbs,[3] Wollstein [4] Mixter [5]). The ultimate results are

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From the Department of Gynecology, Johns Hopkins Medical School and Hospital.

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1. Judd, E. S., and Hand, J. R.: Hypernephroma, J. Urol. **22**:10, 1929.

2. Hyman, A.: A Clinical Study of Malignant Tumors of the Kidney, S. Clin. North America **13**:347 (April) 1933.

3. Kretschmer, H. L., and Hibbs, W. G.: Mixed Tumors of the Kidney in Infancy and Childhood: Study of Seventeen Cases, Surg., Gynec. & Obst. **52**:1, 1931.

4. Wollstein, M.: Renal Neoplasms in Young Children, Arch. Path. **3**:1, 1927.

5. Mixter, C. G.: Malignant Tumors of the Kidney in Infancy and Childhood, Ann. Surg. **96**:1017, 1932.

therefore very unsatisfactory, and in children particularly, in whom large tumors are the rule, the outlook is practically hopeless.

After studying the collected experiences of various clinics, it seems to me that in the vast majority of instances, the failure to cure malignant tumors of the kidney is due to inability to remove the local growth completely. As a rule the disease is still localized when the surgeon operates. In general the history of these cases indicates that the tumor has been present for many months; in the largest reported series in this country, the average duration of preoperative symptoms had been two years. And yet none of these patients had any evidence of metastasis before operation. Too frequently after nephrectomy or exploration, however, there is a rapid local recurrence with a shower of distant metastases. Why is it so difficult to remove these tumors successfully?

Disregarding the important element of operative skill and experience, surgeons agree that the most serious technical difficulties are the size of the tumor, the thinness of the capsule, the extreme vascularity and friability of the mass, the invasion of perirenal structures, extension into the renal vein and the general condition of the patient. Surgeons encounter these handicaps usually in big tumors, for the risk in removing a small hypernephroma, no larger than an orange, is hardly greater than that in a nephrectomy for any other reason, probably not more than 5 per cent. But the mortality that accompanies the removal of massive tumors is so terrific that, even though large growths constitute less than half of the total number, the operative mortality of the whole group varies between 15 and 30 per cent.

Nor does this tell the whole story, for in every reported series a number of cases are found in which nephrectomy was attempted but abandoned because it proved to be too formidable a procedure. These cases are not included in the recorded instances of nephrectomy. The reports of Swan,[6] Hunt,[7] Wollstein [4] and others showed that the cases thus listed as instances of exploratory operations varied between 12 and 26 per cent. In 1933, Hyman [2] stated that the attempt to remove tumors which they formerly dared only to explore doubled their death rate. Furthermore, in another 5 or 10 per cent, no operation whatever was attempted because of metastasis or the extent of the local growth.

Not only is the size of the tumor the chief cause of this forbidding immediate mortality; it also definitely increases the number of local recurrences, in that many of these big tumors are broken during their removal, thus scattering bits of hypernephroma throughout the wound.

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6. Swan, R. H. J.: New Growths of the Kidney, with Analysis of Sixty-Five Cases, Brit. M. J. **1**:606 (April 8) 1933.

7. Hunt, V. C.: Factors of Importance in the Surgical Treatment of Malignant Renal Tumors, Urol. & Cutan. Rev. **36**:291, 1932.

Thus, Judd and Hand [1] stated that in exactly one third of their three hundred and twelve nephrectomies for hypernephromas of all sizes, the capsule of the tumor was ruptured. The fact that practically all late deaths are due to a rapid local recurrence in the wound is sufficient evidence on this point. Also the excessive manipulation of large tumors during their removal favors metastasis, particularly when the renal vessels are not ligated early in the operation.

In general, then, of all patients who on presentation have had renal tumors, from 5 to 10 per cent have been refused any operative treatment because of metastasis or the extent of the local growth; from 12 to 26 per cent have had only exploratory operations; from 15 to 30 per cent have died of operative shock, and of the remainder, less than 10 per cent have been permanently cured.

With these experiences fresh in the memory of every one who has experienced the difficulty of removing large renal tumors or who has had occasion to review the literature, one is inclined to agree with Hyman [2] that "but little progress has been made in improving our percentage of cures."

Up to the present time, surgeons have been powerless in attacking these difficulties. It is true that they have learned the value of repeated transfusions of blood in building up the general condition of the patients, for this is now universal practice. Although it has probably saved some lives, its value is limited and its effect transitory because it may be rather difficult to accomplish much in restoring strength to a person who has an enormous malignant tumor and who is losing blood in the urine almost as fast as one dares to replace it by transfusion.

The one factor which has probably been responsible for more operative deaths than all others combined, the size of the tumor, has remained beyond control until the present time; now, however, in high voltage roentgen therapy, it is hoped that a means has been found of either eliminating or lessening this handicap. And it is my purpose to relate the experience of my associates and myself in trying to accomplish this result.

Roentgen therapy has been used in the treatment of renal tumors in several clinics, but almost exclusively after nephrectomy. Hunt,[7] in 1932, stated that "in extensive, well advanced lesions in which nephrectomy is contemplated, benefit probably occurs sufficiently often to justify preoperative and postoperative radiotherapy." He cited no specific instances, however, in which preoperative roentgen therapy was tried. In 1931 Kretschmer and Hibbs [8] reported a series of seventeen cases of Wilms' tumor in children, in one of which they used preoperative irradiation with some benefit. The child was operated on twice. At the first operation it did not seem possible that the tumor could be removed, and consequently, after a biopsy had been made, the

effort was abandoned. Roentgen treatments were then given which reduced the size of the tumor to such an extent that three and a half months later, nephrectomy was performed. Unfortunately, the child died four months afterward. Although postoperative irradiation was used rather frequently in this series, this was the only instance in which Kretschmer mentioned its use before operation. Neither Kretschmer nor Hunt seemed to find postoperative irradiation very beneficial.

My experience with preoperative irradiation has been striking. In the four cases in which I have used it, the enormous tumors seemed to shrink almost miraculously. And this decrease in size was usually accomplished within three weeks. Of my cases, two presented typical Grawitz hypernephromas, one in a girl of 2½ years, the other in a woman of 51; the other two growths were Wilms embryomas in children of 3 and 16 years. The rate and amount of decrease in the size of these tumors are shown in the illustrations.

By reducing the size of the tumor, the magnitude of the operation is greatly lessened. In addition, it is possible that this may diminish the likelihood of recurrence because the operation is made so much easier and can be done so much more cleanly. The smaller tumor can be removed with little manipulation or bleeding and with a much wider margin. It enables the surgeon to locate and tie the renal pedicle before disturbing the tumor, if the operation is done transperitoneally.

Furthermore when one examines a tumor which has been irradiated successfully, one cannot fail to be impressed by the extensiveness of the cellular destruction. Parts of the tumor consist of hyalinized tissue. In other areas the nuclei are small and pyknotic, the cells have lost their membranes, many have disintegrated, the architecture of the tumor has been destroyed and one gains the impression that the malignant process has been dealt a stunning blow. This is readily seen in the accompanying illustrations.

As will be pointed out, although irradiation may cause part of the tumor to melt away and may remarkably alter its morphology, the treatment does not destroy the tumor completely nor does it change its essential character, for the remaining part shows living malignant cells and prompt growth if it is not removed. Irradiation is therefore merely a useful adjunct in operative preparation, and cannot be expected to eliminate the malignancy. The tumor must be removed if the patient is to be cured.

OPERATION

Preparation.—With this experience, my associates and I have entirely changed our whole method of attacking these large neoplasms and also have revised our regimen of preparing the patient for the ordeal of nephrectomy. We now think that there is an excellent chance of bringing the patient through the operation successfully. It will be interesting to follow the subsequent course of these patients.

Our first object is to make the tumor operable by reducing its size through high voltage irradiation. Otherwise we know our chances are practically zero.

But even before irradiation is started, it may be necessary to give one or two transfusions, because the hematuria and toxemia may have produced a marked degree of anemia, hyperpyrexia and emaciation. If the large tumor has not affected the general health appreciably, we proceed with the irradiation immediately.

The course of irradiation usually lasts about three weeks, and during this time the patient must be under constant medical supervision. It is necessary to examine the blood repeatedly, because irradiation often produces anemia and leukopenia. These complications are met by transfusion and cessation of irradiation. In one of our cases, the white blood cell count dropped to 2,000 during the course of irradiation. We therefore discontinued the treatment immediately even though hardly half of the desired dosage had been utilized. In spite of this, however, the tumor had shrunk to approximately one-sixth its former size.

Gastro-intestinal symptoms may be present but are not disturbing. On the contrary, as the huge abdominal mass recedes, the appetite returns and it again becomes possible for the patient to eat with relish. When one sees how rapidly the mass is disintegrated and absorbed, one wonders what becomes of it and is surprised that the constitutional reaction is not more marked.

Severe hematuria may be a difficult problem. As a rule it diminishes after irradiation begins to take effect. In one of our patients, however, the urine remained blood-red until we irrigated the kidney with a solution of silver nitrate and enforced complete rest in bed.

Throughout the course of irradiation and after its conclusion, we make every effort to bring the patient to the peak of physical condition by diet, rest, tonics and sunshine. We have had no real difficulty in accomplishing this. We have postponed nephrectomy until we felt that the general condition made the operation safe.

The effect of this new operative regimen in the treatment of large renal tumors can be seen in the accompanying reports of cases. I hesitate to present a proposition which may be as important as this when it is supported by only limited experience. These patients, however, have all been observed in my own practice in the last three years and each has been thoroughly studied. In all but one instance, the roentgen therapy has been administered by Dr. Charles A. Waters. Those who are interested in the technic of these treatments are referred to his recent article on this subject.[7a]

Transperitoneal Nephrectomy.—The operative technic is also a matter of vital importance. Most urologists have been trained to carry out their operative procedures on the kidney through a lumbar incision. But for the purpose of removing tumors of the kidney the transperitoneal operation seems to be infinitely superior. The object of the operation is to remove the tumor intact with as much perirenal tissue as possible and with a minimum of handling and manipulation, for one knows how friable and vascular these tumors are and how frequently they invade the renal vein and its smaller intrarenal branches. Through a lumbar incision it is impossible to remove a renal tumor without extensive handling, and the last attachment to be controlled is the vital renal pedicle after the tumor has been exposed and delivered. This violates every object of the operation.

By the transperitoneal route, the whole process is reversed. Through a long rectus incision the peritoneal cavity is opened; the posterior layer of peritoneum lateral to the large intestine is cut, and the intestine is rolled medially. This imme-

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7a. Waters, Charles A.; Lewis, Lloyd G., and Frontz, W. A.: Radiation Therapy of Renal Cortical Neoplasms, South. M. J. **27**:290 (April) 1934.

diately brings one down to the capsule of the tumor. Further mobilization of the intestine and blunt dissection around the hilus of the kidney expose the renal pedicle which can be ligated and cut before one handles the tumor at all. Aberrant vessels can be seen easily because the exposure gives one a complete view of the whole flank and its contents. The tumor, thus deprived of its vascular connections, can then be removed without loss of blood or fear of disseminating metastases. Walker[8] advocated the principle of this operation in 1905, and Finney performed the operation with success and permanent cure twenty years ago. Our experience with both methods of approach compels us to agree with Finney that the extraperitoneal operation is the only method by which to remove a tumor of the kidney. It is a clean and scientific surgical procedure. In our last two patients, hemostasis was so complete and the wounds so clean that the abdomen was closed without drainage. The wounds healed by first intention, and the convalescence was normal.

REPORT OF CASES

To illustrate the proposition advanced in the foregoing portion of the article, I present a series of seven malignant renal tumors that have come under my care in the last three years. These are divided into three groups: first, large tumors in which nephrectomy was performed or attempted without preoperative irradiation; second, large tumors which were removed after preoperative irradiation, and third, small tumors that were removed without irradiation.

Group I: Massive Tumors Not Receiving Preoperative Irradiation.—This group comprises cases 1 and 2.

CASE 1.—*Diagnosis, a large hypernephroma of the left kidney, Grawitz type. Transperitoneal nephrectomy, October 1930. Death, three hours after operation.*

Mrs. K. W., aged 34, residing in Pennsylvania, had been under my care in 1927 for sterility, having been referred by Dr. Sydney R. Miller. A normal child was born in June 1930. She was delivered by a competent obstetrician, but apparently did not return to him for any postnatal observation. I examined her on Dec. 30, 1929, when she had been pregnant for about three months, and at that time one could not feel either kidney.

The case is particularly instructive because of the unusual rapidity with which the tumor must have developed after the birth of the child in June 1930, for when the baby was only 3 months old the patient returned to Baltimore wondering why her abdomen was getting larger instead of smaller. At that time casual inspection showed that she had a big tumor which filled three fourths of the abdomen. There had been no discomfort whatever, no hematuria and no loss in strength. The mass had grown so rapidly that I could hardly persuade myself that it was a solid tumor.

This case is another instance of the fearful operative toll in these big tumors. At operation in the Union Memorial Hospital the capsule of the mass was thin and intimately adherent to the peritoneum, the perirenal structures and the diaphragm. The capsule was broken, and the tissue of the tumor was implanted everywhere (fig. 1). There was no bleeding from the renal pedicle, but the

8. Walker, G.: Transperitoneal Ligation of the Renal Vessels, J. A. M. A. **45**:1647 (Nov. 25) 1905.

enormous vessels that covered the tumor bled profusely. The tumor was removed through a long transperitoneal incision. The patient died of shock three hours later.

CASE 2.—*Hypernephroma of the right kidney, Grawitz type; diagnosed by biopsy, January 1932.*

Mrs. C. D., aged 51, had been discharged from a Baltimore hospital, where an exploratory laparotomy and biopsy revealed a huge hypernephroma. The husband had been told that nothing more could be done and that the outlook was hopeless. Through one of my friends, a house officer in the Johns Hopkins Hospital, he appealed to me for any suggestion. Without offering any hope whatever, I suggested that they might try high voltage roentgen therapy. The patient was therefore sent to the Hospital for Women, where the roentgenologist, Dr. Waters, took charge.

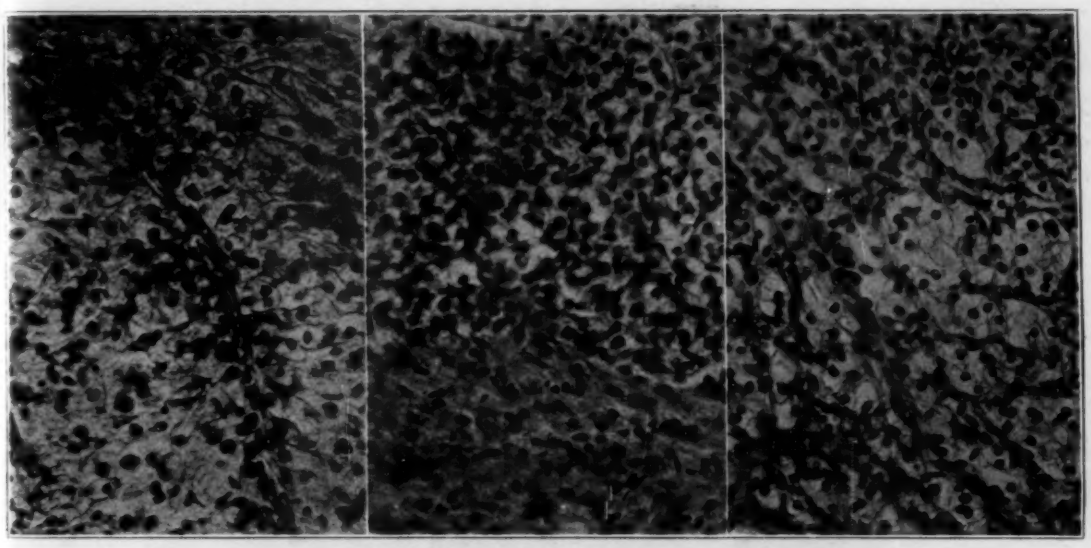

Fig. 1.—High power details of three hypernephromas of the Grawitz type from cases 6, 7 and 1, respectively. These tumors did not receive irradiation. This illustration should be compared with figure 5, which shows the same type of tumor after irradiation.

At the former operation, the tumor was found to fill the entire right half of the abdomen and to extend over into the left. The capsule of the tumor had been broken during the exploration of the mass and particles of the tumor scattered in the peritoneal cavity and abdominal wall. The right rectus incision had been closed after performance of a biopsy.

When the patient was admitted to the Hospital for Women six weeks later, her condition was precarious. The tumor extended from the seventh rib down to the pubis and across the midline of the abdomen (fig. 2). A recurrence of the growth soon developed in the abdominal incision, flank and iliac fossa. The temperature occasionally reached 104 F., the hemoglobin was 50 per cent, and the red blood cells numbered 3,000,000. Dr. Waters gave her a course of three transfusions and high voltage therapy. He asked me to see her in March 1932. By

that time the tumor had receded to a point three fingerbreadths above the anterior superior spine. I advised further roentgen therapy and observation.

For the last two years, we have been watching this woman. She enjoys excellent health and has regained her strength completely; her blood is perfectly normal, and she has no discomfort except occasional attacks of abdominal pain which simulate partial intestinal obstruction. The mass has gradually decreased in size, so that now it extends only about three fingerbreadths below the costal margin in the lumbar fossa. There is, however, a persistent induration of the abdominal wall of the right flank down to the anterior superior spine and extending back to

Fig. 2 (case 2).—Pyelogram showing a hypernephroma of the right side. The tumor was explored with biopsy in January 1932. The roentgenogram outlines the mass which filled the right half of the abdomen. Ninety per cent of this tumor disappeared after irradiation, and it would be easily operable if it were not for multiple implantations in the wound, peritoneum and lumbar fossa caused by premature exploration and biopsy. No metastases have occurred in almost three years, and the general health is good.

the erector spinae muscles. In the last month, I have thought that this induration has increased.

Through the last two years, we have been considering the advisability of removing this tumor, but have always decided that it would be futile. The diffuse induration in the flank and iliac fossa probably represents an active hyper-

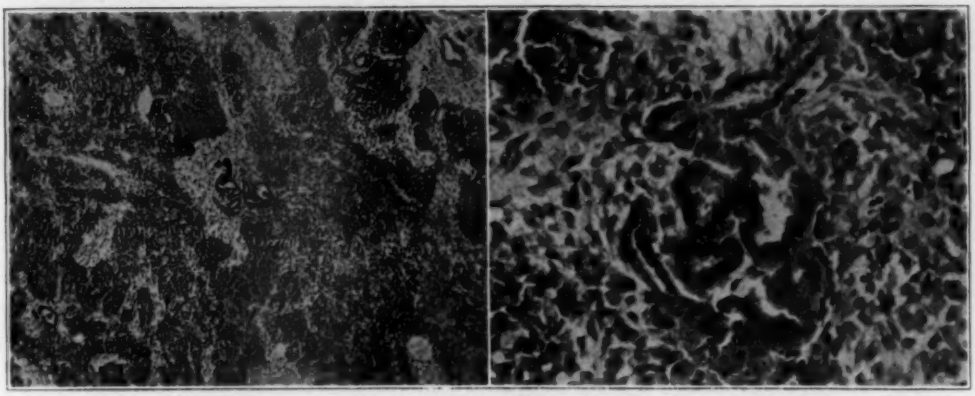

Fig. 3 (case 3).—Embryoma, Wilms' type, before irradiation. Note the solid masses of cells resembling those of a sarcoma, in which are scattered tubular masses. Compare this with figure 4.

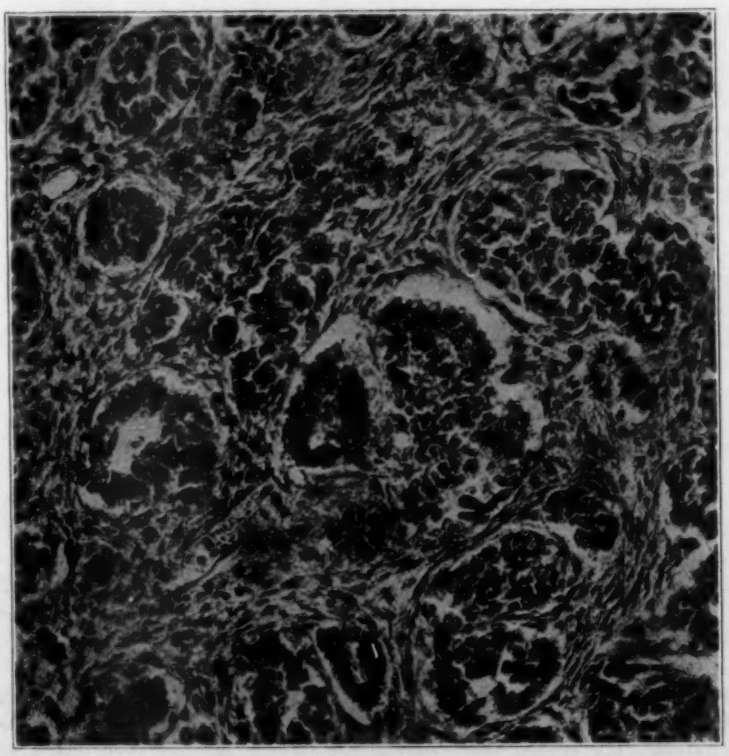

Fig. 4 (case 3).—Embryoma, Wilms' type, the same tumor as seen in figure 3, after irradiation and removal. Although the destructive effect of irradiation is not striking histologically, the decrease in the size of the tumor was perfectly satisfactory.

nephroma which would only be transplanted and stimulated by an operation. Furthermore, this patient has an extremely high blood pressure. For the time being, therefore, we have decided not to try to remove this growth, believing that she will live longer and more comfortably if it is controlled occasionally by roentgen therapy. If this tumor had not been explored and disseminated, it would have been easily operable.

Group II: Massive Tumors Removed After Preoperative Irradiation.—In this group are cases 3, 4 and 5.

CASE 3.—*Diagnosis, a large Wilms' tumor of the right kidney. Exploratory operation and biopsy, November 1933. Nephrectomy, January 1934.*

E. F., a child of 3 years, was seen at St. Joseph's Hospital in November 1933, ten days after nephrectomy had been attempted by another surgeon. He exposed the tumor through the lumbar incision without preoperative irradiation. The mass filled half of the abdomen. It was decided that the tumor could not be removed and, therefore, after a biopsy was made the wound was closed (fig. 3). When I was asked to see the child ten days later, it was evident that the only chance lay in reduction of the size of the tumor by irradiation. This was promptly begun by Dr. Howard E. Ashbury, the radiologist. Within one month this tumor was palpable only in the right renal fossa, and the general condition of the child was excellent. On Jan. 15, 1934, the tumor was removed by the surgeon in charge (fig. 4). The damage of the former biopsy, however, was evident in the dense adhesions. The tumor was again ruptured during its removal and it had to be cut away from the old wound in the lumbar fossa. In this case I feel that the chance of cure has been definitely lessened by the premature biopsy.

CASE 4.—*Diagnosis, hypernephroma of the right suprarenal gland, Grawitz type; normal kidney. Right nephrectomy and removal of the right suprarenal gland and tumor, Oct. 12, 1933.*

When C. S., a Negro girl, 2½ years old, was admitted to the Provident Hospital in August 1933, she had evidently only a short time to live. She was emaciated, and her temperature was 105 F. The abdomen was distended by a huge mass which crossed the midline and filled every quadrant except the left iliac fossa and the extreme left side. The hemoglobin was around 50 per cent and the red blood cell count below 3,000,000. The mother had noticed the tumor three months before, but did not bring the patient to the dispensary of the hospital for the colored until the child became emaciated. There had been no hematuria. There was sexual precocity; the pubic hairs were well developed.

It was obvious that the child was in no condition for either operation or irradiation. Repeated small transfusions were therefore given, and eventually a course of intense, but carefully measured roentgen therapy was carried out. The effect was miraculous. Within three weeks, nine tenths of the tumor had gone (figs. 5 and 6), and one could just feel it below the costal margin in the right lumbar region. Irradiation was continued for about a month.

The medical care was conducted by Dr. Lawson Wilkins, the consultant in pediatrics at the Provident Hospital. By Oct. 12, 1933, or in about seven weeks from the time of admission, we thought that the condition warranted the risk of the operation. The hemoglobin had reached 70 per cent, the mass could not be felt at all and the child was apparently in perfect health.

The operation was easily performed, although we were surprised at what we found. We used a long right rectus incision which gave perfect exposure to the whole right flank. The right kidney was completely normal, but behind and above

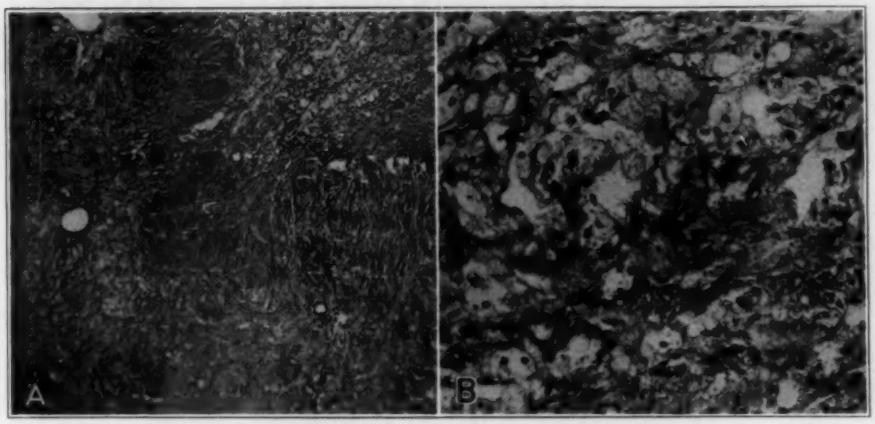

Fig. 5 (case 4).—Hypernephroma, Grawitz type, after irradiation. Notice the areas of hyalinization, pyknosis, deposit of pigment, destruction of the architecture of the tumor and cellular degeneration. (Photomicrograph on the left, × 100; that on the right, × 300.)

Fig. 6 (case 4).—Hypernephroma, Grawitz type, of the right suprarenal gland in a girl of 2½ years. The rapid decrease in size of the tumor following irradiation is shown. Thirteen days after irradiation was begun, the tumor could be just felt under the ribs. Figure 5 shows the histologic appearance of this tumor.

it lay a mass of almost exactly the same size and shape as the kidney itself. It was adherent to the posterior surface of the kidney but distinctly separate from it. The mass was attached by a broad pedicle high up and behind the renal pedicle. The tumor was rather firm, enclosed in a dense fibrous capsule and not particularly adherent to the dipahragm or the walls of the lumbar fossa.

The vessels of the kidney were clamped and ligated before we had mobilized the kidney at all, or before we were aware that the tumor was connected with the suprarenal gland. As we mobilized the kidney we saw that the mass was behind it. We removed the kidney first, thus obtaining an excellent view of the suprarenal gland and the tumor. After liberating the tumor the pedicle was clamped and the entire mass removed (fig. 7). There was no bleeding or shock.

The convalescence was uneventful. It is, of course, impossible to predict the future for this child. Before operation, with the tumor she weighed 27 pounds (12.2 Kg.); one month later she weighed 32 pounds (14.5 Kg.). She appears to

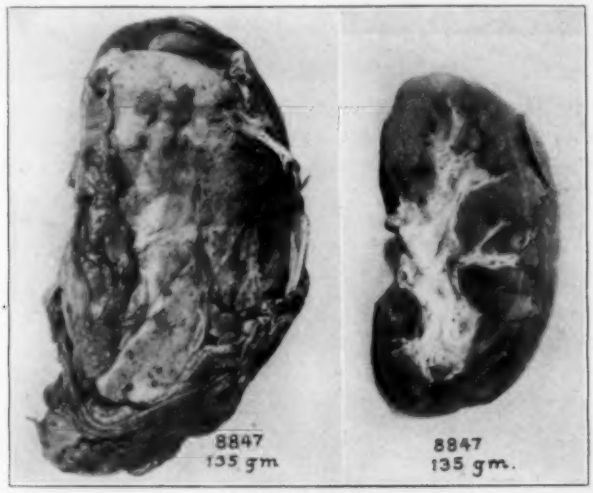

Fig. 7 (case 4).—Hypernephroma of the right suprarenal gland and the normal right kidney removed with it. Each weighed 135 Gm.

be perfectly well. We are arranging to have her return for observation every month until we are satisfied that the danger of recurrence is past.

CASE 5.—*Diagnosis, a large Wilms' tumor on the left side.*

Miss B. M., aged 16, first noticed blood in the urine during the summer, 1932, but was not referred for diagnostic study until August 1933. By that time, the patient had become emaciated and had an abdominal mass which looked like an advanced pregnancy. When I saw her in August 1933, she was so weak that she could hardly get out of bed and was very thin and pale. One could see the prominent mass which extended from the left flank across the midline to the region of the gallbladder and thence down below the umbilicus toward the pelvis (fig. 8). A blood count showed: red cells, 3,200,000; white cells, 2,200, and hemoglobin, 45 per cent. The urine was red with blood. The patient was immediately sent into the Church Home where a transfusion was given. By the usual urologic means, the diagnosis of renal tumor was made; no metastases were evident radiologically or clinically.

We experienced considerable difficulty in restoring this girl to a satisfactory physical state because of the profuse hematuria and the leukopenia. The hematuria persisted even after the tumor had been irradiated, and this wiped out the benefit of repeated transfusions. Finally, we controlled the bleeding by renal lavage with a solution of silver nitrate and by complete rest.

The leukopenia was even more troublesome. It was present before the patient received any irradiation (2,200 white blood cells) and became more marked afterward. At no time, however, did differential stains reveal any organic disease of the blood-forming organs. Six weeks after irradiation had been stopped, the white

Fig. 8 (case 5).—Retrograde pyelogram of an embryoma of the left kidney before irradiation. The mass fills most of the upper and left parts of the abdomen.

blood cells numbered 5,600, the differential count was normal and the hemoglobin was 76 per cent.

Because of the leukopenia, however, we stopped irradiation before the desired dose had been given. For this reason, perhaps, the tumor did not shrink as completely as it might have done otherwise. Nevertheless, as shown in figure 9, the entire abdominal mass disappeared, leaving only the mass in the flank and under the diaphragm.

The improvement in the general condition was also remarkable. During the first month after irradiation, the girl gained 16 pounds (7.3 Kg.) and looked and

Fig. 9 (case 5).—Intravenous pyelogram taken of the tumor after irradiation. The abdominal mass has entirely disappeared; there is still a mass under the diaphragm as large as a child's head. The pelvis of the kidney before irradiation was opposite the fourth and fifth lumbar vertebrae (compare figure 8); after irradiation, it lies opposite the second and third lumbar vertebrae.

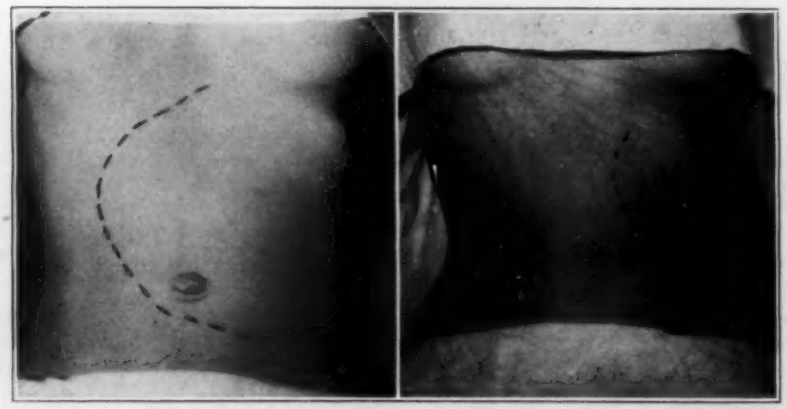

Fig. 10 (case 5).—Embryoma of the Wilms' type in the left kidney of a girl of 16. The remarkable decrease in the size of the tumor in eighteen days was accomplished with half the usual roentgen dosage. See the text, figures 8 and 9, for pyelograms taken before and after irradiation, and figure 11 for histologic characteristics.

felt perfectly well. We were compelled to defer operation, however, beyond the optimum time because of the reluctance of the parents. During this month of procrastination, the tumor definitely increased in size. The patient herself settled the question of operation when she had a recurrence of severe hematuria seven weeks after the course of irradiation had ended.

A left transperitoneal nephrectomy was performed at the Church Home on Nov. 27, 1933. This case, like the preceding one, stands out in sharp contrast to those in which irradiation was not given. Although we had to remove a tumor as large as a man's head, the long left rectus incision gave us excellent exposure to the tumor and the renal pedicle, for the abdominal mass had disappeared entirely. The pedicle was ligated before the tumor was mobilized. There were several large aberrant vessels which were seen clearly and ligated. The suprarenal gland was almost enveloped by the tumor, and it was removed with the tumor in one mass. The patient was on the operating table about an hour and fifteen minutes. The convalescence was uneventful.

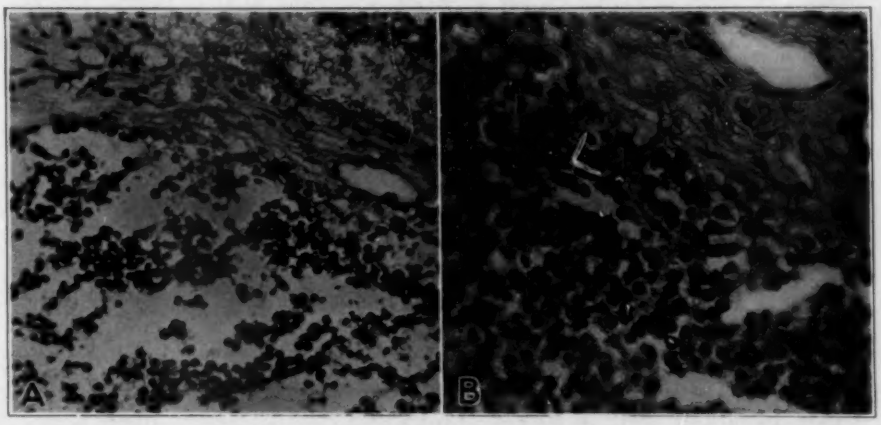

Fig. 11 (case 5).—Embryoma, probably of the Wilms' type, after irradiation. Here again the destructive action is evident although only half the desired dose of irradiation could be utilized. (Photomicrograph on the left, × 55; that on the right, × 300.)

Group III: Small Tumors Removed Without Irradiation.—These cases are presented for three reasons: to show the ease with which a small hypernephroma can be removed; to commend the example of the general practitioners who recognize the seriousness of hematuria, and to contrast the pathologic structure of tumors before and after irradiation.

CASE 6.—*Diagnosis, hypernephroma of the right kidney, Grawitz type. Extraperitoneal lumbar nephrectomy, Jan. 9, 1932.*

Mrs. M. R., aged 52, entered the Union Memorial Hospital with the complaint of a painless hematuria, which had been noticeable for only three days. Six months previously, the urine had been examined by her family physicion, Dr. James Akehurst, and found to be normal. It is interesting that three years previously I performed a panhysterectomy on this woman's sister for carcinoma of the body

of the uterus, and so far there has been no recurrence. The family doctor sent her for a cystoscopic study as soon as he discovered the hematuria.

By the usual cystoscopic studies, we made a diagnosis of hypernephroma, and on Jan. 9, 1932, we removed the right kidney. The tumor was small, not more than 5 cm. in diameter (fig. 1). The operation was easily performed. The convalescence was uneventful and the patient has shown no evidence of recurrence.

CASE 7.—*Diagnosis, hypernephroma of the left kidney, Grawitz type. Left lumbar nephrectomy, March 3, 1932, Sinai Hospital.*

Mrs. M. R., aged 48, like the patient in case 6, had had hematuria for only a short time, four days. It had been accompanied by a dull ache in the region of the left ureter and kidney. There were no other symptoms. Again the family physician, Dr. Samuel Whitehouse, demanded immediate investigation as soon as the hematuria was reported to him.

After the usual cystoscopic procedures (bilateral pyelograms, functional tests, cultures and urinalysis) the diagnosis of a hypernephroma of the left side was made. In this case, however, the diagnosis was made in spite of two sets of pyelograms which showed no sure sign of tumor. Since the patient had unilateral, unexplainable hematuria and since I could just feel the lower pole of the left kidney, I decided that we were dealing with an enlarged left kidney and probably an early hypernephroma (fig. 1). On March 3, 1932, I removed the tumor and thus far there is no evidence of recurrence.

SUMMARY

In summarizing my own experience with the surgical removal of renal tumors in the last three years, I cannot escape the conclusion that life has been prolonged and probably saved by the use of preoperative irradiation. The histories of five patients with massive malignant tumors have been presented. Three of these patients were operated on by different surgeons in Baltimore without preoperative irradiation. All three operations were failures; one patient died of shock three hours after nephrectomy and the other two had only biopsies. I have presented a group of four cases of massive tumors that were treated by high voltage roentgen therapy for the purpose of decreasing their size so that they might be removed in safety. Two of these tumors were operated on without any complication or difficulty whatever. Both of these were in children, among whom the mortality has always been very great. The third tumor, which had previously been explored and declared inoperable, was later irradiated successfully and removed, but the harm done by the premature biopsy was probably beyond repair. The fourth large tumor was also explored prematurely, but has since been largely destroyed by irradiation. I fear, however, that in this case also, the dissemination of the tumor by the biopsy has made the situation hopeless.

The last two cases of small hypernephromas were included merely to reinforce the statement that the most serious single handicap in the removal of renal tumors is their great size. Small tumors usually offer little operative difficulty.

CONCLUSIONS

1. A review of the literature shows that up to the present the results in the surgical treatment of renal tumors have been highly unsatisfactory. From 5 to 10 per cent of the patients are refused operation because of the evident metastasis or the apparent impossibility of removing the local growth; from 12 to 26 per cent have only exploratory operations; from 15 to 30 per cent die of surgical shock after nephrectomy, and of the remainder, less than 10 per cent are permanently cured.

2. The greatest single cause of this high mortality is the enormous size of these tumors, which prevents complete surgical removal, causes a high operative death rate and favors local recurrence and metastasis.

3. In my experience, preoperative irradiation of both Wilms' and Grawitz' tumors causes a remarkable decrease in their size and makes them easily operable.

4. Preoperative irradiation also causes definite cellular changes in the malignant tissue, such as hyalinization, pyknosis, fragmentation and destruction of the architecture of the tumor.

5. Irradiation, however, will not destroy malignant tumors entirely. After having been intensively irradiated, tumors which I have removed have uniformly shown living malignant tissue; those which I have not removed have resumed active growth. Roentgen therapy is only a means of preparation to make the tumor operable, or a palliative measure to hold in check a tumor which cannot be removed.

6. The experience of my colleagues and myself with preoperative irradiation of massive renal tumors has caused us to institute an entirely new regimen in preparing these patients for operation.

7. I cannot urge too strongly the advantages of the transperitoneal approach as the most logical, clean and surest way to remove tumors of the kidney.

Dr. Arnold R. Rich, associate professor of pathology in the Johns Hopkins Medical School, studied the sections from some of these tumors, particularly those which had been irradiated.

1201 North Calvert Street.

HEMORRHAGIC VILLOUS SYNOVITIS OF THE KNEE JOINT DUE TO XANTHOMA

REPORT OF A CASE

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The occurrence of hemorrhagic effusion into the knee joint due to xanthoma is very uncommon. In a review of the literature only five cases have been reported. In view of the extreme rarity of this condition we are reporting the following case.

REPORT OF CASE

History.—W. M., aged 23, white, American born, a garage hand, was admitted to the service of Dr. Harry Finkelstein, Hospital for Joint Diseases, New York, on March 7, 1932, suffering from a painful swelling of the left knee, which had increased in size during the past two years. There was no history of trauma.

He had had occasional pain in the shoulders since the age of 13. He had gonorrhea in 1930, for which he received treatment and was discharged as cured. Appendectomy was performed in 1920. His parents and one brother and sister were in good health. There was no family history of arthritis, tuberculosis or hemophilia.

Physical and Laboratory Examinations.—The patient was well developed and well nourished, but somewhat pale. The physical findings were insignificant except for the local condition. The left knee joint was enlarged with some increase of local temperature. There was ballottement of the patella, with definite fluctuation in the joint. The range of motion was decreased. The roentgenograms, taken outside of the hospital two weeks before admission, showed nothing abnormal.

Aspiration from the left knee joint yielded 50 cc. of a frankly bloody fluid of a thick consistency.

Tests for the Wassermann and gonorrheal complement fixations in the fluid and blood and the inoculation of a guinea-pig gave negative results.

Seven days later, March 14, the fluid had reaccumulated and by a second aspiration a hemorrhagic fluid was again recovered. The knee was strapped. Four days later there was a recurrence of the fluid in the knee and a third aspiration of hemorrhagic fluid was performed. The knee was again strapped and rest in bed was advised. The icterus index of the fluid was 58.8. One week later (March 25) the fluid had reaccumulated, and a fourth aspiration yielded 60 cc. of hemorrhagic fluid. After the aspiration a freely movable body, the size of a cherry, was felt over the head of the fibula. The icteric index in the joint fluid was 50.

From the service of Dr. H. Finkelstein, Hospital for Joint Diseases, New York.

Urinalysis gave negative results.

Examination of the blood showed the bleeding time to be two minutes; the coagulation time, one and a half minutes.

A complete blood count gave the following results: hemoglobin, 85 per cent; red blood cells, 4,540,000; white blood cells, 12,200; neutrophils, 59 per cent; eosinophils, 2 per cent; lymphocytes, 27 per cent, and monocytes, 2 per cent.

Tests for the fragility of the red blood cells showed initial hemolysis in a 0.42 per cent saline solution, complete hemolysis in a 0.38 per cent solution.

The roentgenograms of the left knee showed nothing abnormal.

The diagnosis of a villous hemorrhagic synovitis with a possible polyp was made, and the patient was admitted to the hospital for operation. Although the fluid had reaccumulated, the knee was free from pain and motion was normal. The circumference of the left knee was 14 inches (35.5 cm.); that of the right, 13½ inches (34.3 cm.).

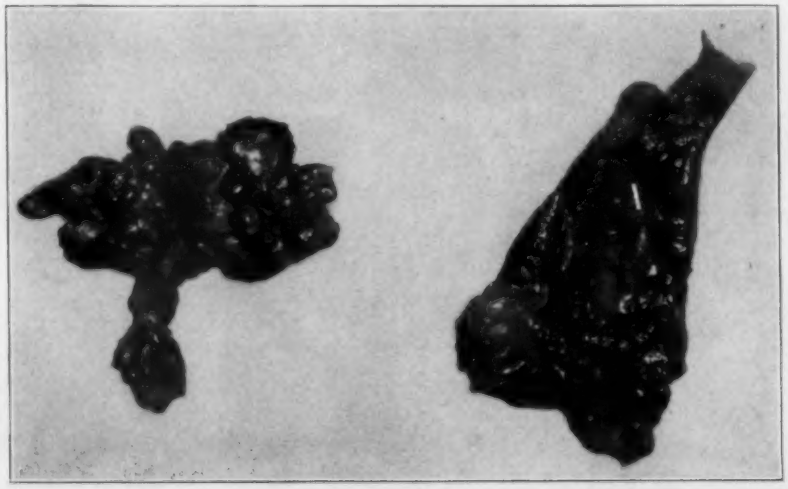

Fig. 1.—Portions of the synovial membrane showing the synovia thickened and diffusely studded with villi. The dark areas seen in the section were a dark reddish brown.

An operation was performed on April 7.

Operative Procedure.—An arthroscopy and synovectomy were performed. The arthroscopy by Dr. Burmann showed an excessive amount of bleeding when the nick in the skin was made previous to introducing the instrument. Bloody fluid escaped from the trocar and could be partially cleared only by repeated washing. The joint appeared to be filled with dark brown fibrin. The infrapatellar pad of fat protruded into the joint and the internal condyle was brownish.

A synovectomy was then performed by one of us (Dr. Sashin). A parapatellar incision was made extending from the tibial tuberosity to the apex of the pouch of the quadriceps. The knee joint was found to be filled with a fibrinous clot and adhesions. The synovia was dark red or brownish and thickened. Masses of hemorrhagic polypoid villi were found in the quadriceps pouch. The menisci, crucial ligaments and articular surfaces were found intact. All of

the accessible synovia was removed (fig.1). One large vessel was secured by a deep suture. The wound was closed in layers with chromic gut for the deeper tissues and silk for the skin. A compression dressing was applied with a molded posterior plaster splint.

Microscopic Examination (Dr. Jaffe).—Sections showed a hypertrophied synovia with the formation of villi. The hypertrophied folds contained large numbers of newly formed blood vessels with considerable blood pigment and some giant cells (figs. 2 and 3). As yet there was no great number of phagocytes. The vascular appearance did not indicate that the lesion was primarily an angioma. The primary cause of the lesion could not be demonstrated in the slide. It was related to the polymorphocellular, xanthoma-like or angioma-like

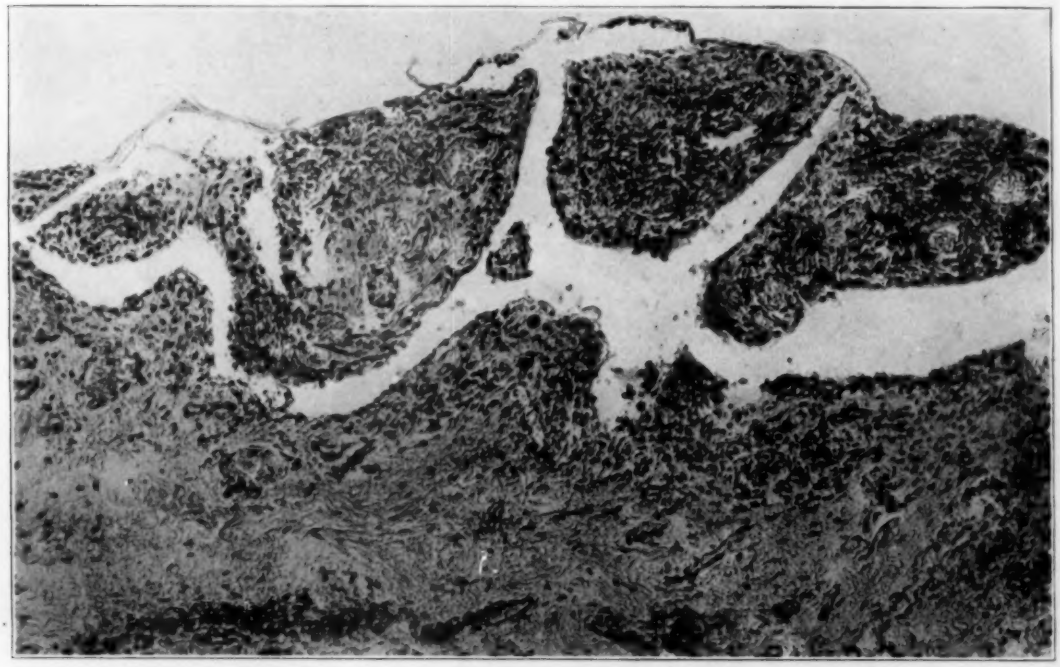

Fig. 2.—Low power magnification of a section showing a hypertrophy of the synovial membrane with the formation of numerous villi.

lesion encountered in the joints, especially the knee joints, and on tendon sheaths, the etiology of which is unknown. The lesion is not a tumor though it is often loosely described as such. As judged from the sections this seemed to be an earlier phase of the type of lesion that may grow to large proportions in the knee joint, complete removal of which produces a cure.

Smears from the synovial membrane showed occasional pus cells and no bacteria. Cultures from the membrane were sterile after four days.

Postoperative Course.—In the evening after operation the temperature rose to 101.8 F. The patient suffered pain in the knee joint and had to be given sedatives. The temperature persisted between 99 and 101.3 F. for about ten days

and returned gradually to normal. On April 12 the posterior splint was removed, and active and passive motion was begun. Motion improved, with no recurrence of fluid.

The patient was discharged on April 23 with extension of the knee to an angle of 180 degrees and flexion up to an angle of 150 degrees. He subsequently received diathermy, massage and exercises for the left knee. Flexion improved to 135 degrees and the treatment was discontinued on June 8.

A check-up examination on August 3 showed the knee to be in excellent condition. The angle of greatest extension was 180 degrees and that of greatest flexion, 125 degrees. There was no pain, tenderness or fluctuation. The patient

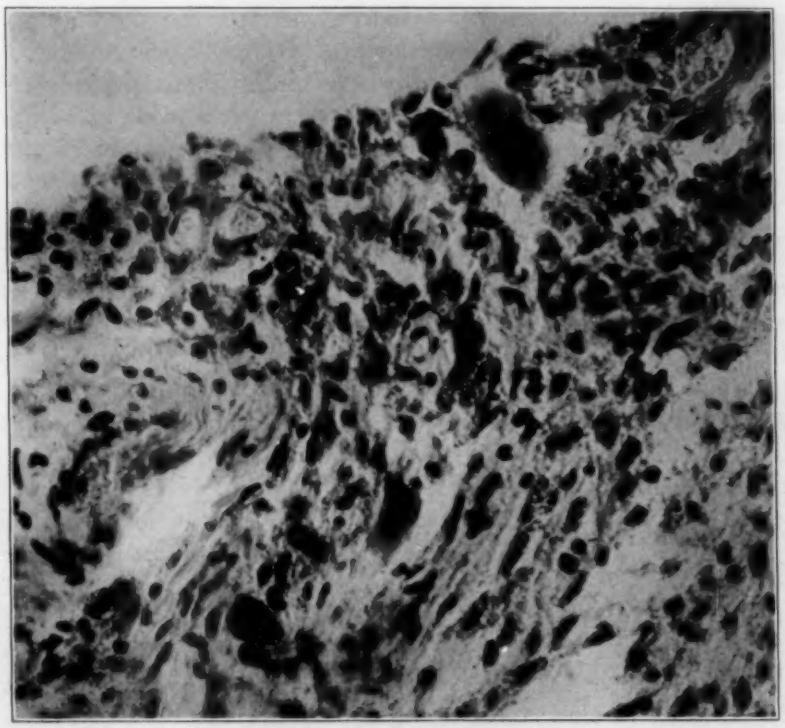

Fig. 3.—High power magnification of a section of synovial membrane showing giant cells, numerous blood vessels and a large increase of synovial cells.

was advised to return in about six months. Reexamination on December 23 showed full range of extension and flexion up to an angle of 70 degrees. The knee was in excellent condition. At this time the cholesterol content of the blood was 288 mg. per hundred cubic centimeters; on March 6, 1933, 240 mg., and on April 15, 238 mg.

COMMENT

The characteristics of this case are as follows: A diffuse, villous, hemorrhagic hypertrophy of the synovia, especially in the suprapatellar pouch, had reached tumor-like dimensions. The dark red and brown color showed the presence of numerous vessels which were easily vulner-

able and had produced old and recent hemorrhages. Yellowish patches, characteristic of xanthoma, were present. Studied microscopically, the villi showed numerous rows of cells of the type seen in the synovial lining and a stroma of fibroblasts, numerous large and small vessels and giant cells. The last-mentioned cells had the characteristics of giant cells of the foreign body type rather than of those of the tumor type. The vesicular nuclei were deeply stained and showed a margin of protoplasm. Lesions of this kind are classified either as tumors or as granulomas. They occur rarely. Only about fifty such tumors have been reported to date. This number includes spindle and round cell sarcomas of the capsule or bone with infiltration of the synovial membrane, and cavernous hemangiomas which also have broken into the joints from the surrounding tissues. The largest single group is made up of interarticular giant cell tumors, also called benign xanthomatous sarcomas of the knee joint.

REVIEW OF LITERATURE

Eric Sonntag [1] has collected twenty cases from the literature. Of these sixteen cases presented localized growths in the synovial membrane of the knee joint. In only four cases were there diffuse lesions comparable to our own case. Among the latter group the first case of Lejars and Rubens-Duval [2] showed different characteristics. The tissue did not contain giant cells, but was made up in some places of spindle cells, and in others of glandlike arrangements of endothelial cells containing mucin. The case of Dowd,[3] published in 1912, should be excluded, as the tissue contained only a moderate number of blood vessels and the fluid in the joint was clear; also the giant cells showed mitotic figures not encountered in the xanthoma. No xanthoma cells were found in this case. The case of Harbitz [4] should not be included in this group as it was that of a diffuse endothelioma, partly calcified and also infiltrating the bone. In this group, therefore, there remains only one case, that of Hartman,[5] described in 1922. The patient was a man of 20, who for four years had complained of pain in the knees. Frequent aspirations revealed bloody fluid. At operation blood was

1. Sonntag, E.: Ueber intraartikuläre Xanthome des Knies, Deutsche Ztschr. f. Chir. **223**:346, 1930.

2. Lejars and Rubens-Duval: Les sarcomes primitifs des synoviales articulaires, Rev. de chir., Paris **41**:751, 1910.

3. Dowd, C. N.: Villous Arthritis of the Knee, Ann. Surg. **56**:363, 1912.

4. Harbitz, F.: Tumors with Xanthoma Tissue, Norsk mag. f. lægevidensk. **86**:321, 1925.

5. Hartman, F. W.: Synovial Membrane Tumors of Joints, Surg., Gynec. & Obst. **34**:161, 1922.

found in the synovial cavity. The synovial membrane was very thick and studded with villi of reddish brown or fawn; the cartilage in the crucial ligaments was also involved. The microscopic sections showed the capsule to be thickened and to contain brownish pigments, large and small villi and an abundance of large and small vessels. The stroma was made up of the following types of cells: monocytes, sometimes with pigments; oval cells, either single or in collections, with small blue nuclei and clear granular protoplasm; occasional giant cells, and, finally, foamy cells which contained double refractive lipoid material from which crystals of cholesterol could be obtained.

A second case of diffuse xanthoma was reported in 1927 by Herxheimer [6] in a woman 30 years of age. Histologically, spindle cells, giant cells and xanthoma cells were found. A third case was reported by Frangenheim [7] in 1928, that of a man of 50 who had suffered a dislocation of the left patella in 1904 and had had intermittent effusions. He was free from disability until 1924, when he noticed a growth in the popliteal fossa. The operation showed polygonal cells, giant cells, hemorrhages and pigment. He had a recurrence after six years, with pain and effusion. At operation the synovial membrane was found to be hemorrhagic and villous, and contained numerous blood vessels and capillaries, giant cells and "osteoid stroma."

In addition two cases described as hemorrhagic villous arthritis by Koch [8] and Mandl [9] belong to this group. Koch's case was that of a girl of 22 in whom pain and swelling of the right knee joint developed in 1924. At operation the synovia was found to be much thickened with large clots of blood in the cavity and thrombosis of the vessels. Histologic examination showed a very vascular tissue with numerous fibroblasts and blood pigment. Three years later there was a recurrence and the patient again submitted to operation. The synovia was found to be hemorrhagic and villous. On microscopic examination, numerous vessels, infiltration of pigment and giant cells of the foreign body type were found. Mandl's case was that of a man of 30, who had suffered an indefinite injury, followed by development of pain and swelling of the knee with occasional locking. Aspiration of fluid from the knee joint was performed fifty times. He received baths, bandaging, and

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6. Herxheimer, G.: Ueber Xanthome und Xanthelasmen, Arch. per le sc. med. **50**:201, 1927.

7. Frangenheim, P.: Das gutartige xanthomatöse Riesenzellensarkom der Gelenkkapsel, Arch. f. klin. Chir. **157**:738, 1929.

8. Koch, H.: Chronische hämorrhagische Arthritis des Kniegelenks, Zentralbl. f. Chir. **54**:2892, 1927.

9. Mandl, F.: Ueber die operative Behandlung chronischer nichtspezifischer Erkrankungen des Kniegelenks, Arch. f. klin. Chir. **151**:302, 1928.

injections into the joint. An operation was done in October 1926. On the medial aspect of the synovial membrane, brownish-red villi were observed, which histologically contained several rows of synovial lining cells, numerous vessels, lymphocytes and plasma cells with much blood pigment. A partial synovectomy was done, but there was a recurrence of symptoms and a second operation was performed a year later. The whole synovial membrane was then found to be covered by brownish-red villi which contained numerous blood vessels, several rows of synovial cells, a large amount of blood pigment and islands of light cells with double refractive protoplasm which gave a positive stain for fat, characteristic for xanthoma.

PATHOGENESIS

The pathogenesis of these conditions is still controversial. The first observers considered them to be tumors of sarcomatous character. In 1898 Dor,[10] who discovered the xanthoma cells, advanced the theory of an inflammatory and traumatic origin for this growth, and was supported by Fleissig,[11] Wustmann[12] and others. Seyler[13] held an intermediate view, and of ten cases he regarded three as granulomas. The arguments for the blastoma theory were well summarized by von Albertini[14] and for an inflammatory origin by Sonntag. Von Albertini regarded the giant cell tumors of the periosteum, bone, tendons and joints as of identical structure. They originate from an embryonal mesenchyme which has not undergone complete differentiation and is, therefore, apt to develop giant cells. The numerous vessels present in these growths are explained by the canalization of loose mesenchymal tissue. The second characteristic element is the xanthoma cell which is found only in giant cell tumors of the tendons and joints, and not in epulides or giant cell tumors of the bone. This can be explained by a disposition of the skin, tendons and joints to precipitation of lipoids. In the multiple xanthomas of the skin this occurs on the basis of a hypercholesteremia, analogous to the formation of tophi in gout. In the solitary giant cell tumors of the joints and tendons, hypercholesteremia

10. Dor, L.: Relations des tumeurs à myeloplaxes et des xanthomes, Compt. rend. Congr. franç. de Chir., 1898, p. 553.

11. Fleissig, J.: Xanthomatöse Geschwülste, Deutsche Ztschr. f. Chir. **192**:380, 1925.

12. Wustmann, O.: Xanthomatous Giant Cell Tumors, Deutsche Ztschr. f. Chir. **192**:381, 1925.

13. Seyler: Ueber xanthomatische Granulome, Virchows Arch. f. path. Anat. **239**:20, 1922.

14. von Albertini, A.: Spezielle Pathologie der Sehnen, Sehnenscheiden und Schleimbeutel, in Henke, F., and Lubarch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 9, p. 556.

was found only in a part of the cases. Kirch [15] collected eight cases in which the cholesterol content of the patients varied between 481 and 173 mg. per hundred cubic centimeters of blood. The normal cholesterol content of the blood varies between 140 and 160 mg. In the cases in which the cholesterol content of the patient's blood was normal, the presence of xanthoma cells was explained by the precipitation of lipoids, especially cholesterol, from a hematoma, or as due to stagnation of circulation and deficiency of absorption. Von Albertini advanced the following arguments against the conception of these growths as granulomas: Only exceptionally are inflammatory granulations found. Bacteria have never been demonstrated in these growths. The giant cells have no relation to the vessels and, therefore, do not originate from the endothelium of vessels, as proposed by Lubarsch.[16] They also are not giant cells of the foreign body type attracted by the precipitation of cholesterol, as the majority do not contain cholesterol in the plasma, and do not accumulate in the vicinity of the precipitation of the lipoids. He, however, admitted that besides genuine blastomatous giant cells there are present giant cells of the foreign body type, chiefly around the blood pigment. He did not regard the experiments on animals as conclusive. Anitschikow [17] and others have produced xanthomatous growths in tendons of animals fed with a diet rich in cholesterol, or animals which had been given intravenous injections of cholesterol and subsequently traumatized. Von Albertini regarded these lesions only as lipophagic foreign body cell granulomas without the characteristics of true giant cell tumors.

Eric Sonntag advanced the following arguments for the theory of the inflammatory origin of the xanthomatous tumors: The stroma of the growths is a typical granulation tissue consisting of fibroblasts, lymphocytes, polymorphonuclear leukocytes, partly sclerotic scar tissue, blood pigment and crystals of cholesterol surrounded by giant cells. The giant cells have vesicular, only faintly stained nuclei and a definite protoplasmic border. Blastoma giant cells have oval, heavily stained nuclei, and they do not show protoplasmic borders. Both authors agreed, however, that the xanthomatous cells in these growths are only secondary, and are produced in response either to a hypercholesteremia or to a local disturbance of lipoid metabolism.

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15. Kirch, E.: Ueber cystische xanthomatöse Geschwülste und die Genese des xanthomatösen Geschwülste im allgemeinen, Beitr. z. path. Anat. u. z. allg. Path. **70**:75, 1922.

16. Lubarsch, O.: Generalisierte Xanthomatöse beim Diabetes, Deutsche med. Wchnschr. **18**:484, 1918.

17. Anitschikow, N.: Ueber experimentell erzeugte Ablagerungen von Cholesterinestern und Anhäufungen von Xanthomzellen im subkutanen Bindegewebe des Kaninchens, München. med. Wchnschr. **40**:2555, 1913.

DIAGNOSIS AND TREATMENT

The general symptoms of this condition are not characteristic. The patient complains of a swelling of the knee joint, pain, a limp in walking and sometimes of locking of the knee joint. The onset is insidious. Only part of the patients give a history of a definite injury. On examination, swelling, limitation of motion and fluctuation are found. In localized tumors a definite mass, more or less freely movable, can be palpated. The symptoms are therefore not different from those in an internal derangement or inflammatory condition. Most of the patients therefore come to operation with a diagnosis of loose cartilage or tuberculosis of the knee joint.

The diagnosis, however, can be definitely established by an aspiration and thorough examination of the joint fluid. Most authors mention the finding of blood in the cavity of the joint at operation, but not enough emphasis is placed on aspiration of joint fluids. The finding of hemorrhagic fluid without recent injury in conjunction with the bilirubin content of the effusion furnishes a conclusive diagnosis of hemorrhagic, villous synovitis. One of use (Kling [18]) has pointed out that a hemorrhage in the joint cavity is finally broken down to bilirubin. A high content of bilirubin is, therefore, proof of an older hemorrhage in the joint. In our case the icteric index was between 58.8 and 50 in subsequent aspirations, the normal content of bilirubin in joint fluids being below 5. This means a rise in the content of bilirubin in our case to about ten times the normal, proving that the aspirated blood originated from a spontaneous hemorrhage and was not due to a lesion of a vessel during aspiration. The almost constant level of the bilirubin in several aspirations showed that a constant bleeding was occurring into the joint cavity. A high content of cholesterol in the synovial fluid would establish the presence of xanthoma conclusively. The tissue in our case had the characteristics of the giant cell tumors. The synovia was much thickened, villous, hemorrhagic and in places yellowish owing to precipitation of lipoids. The sections showed that the villi were lined by several rows of synovial cells; the stroma contained large amounts of newly formed blood vessels, much blood pigment and giant cells. The high cholesterol content of the blood (288 mg. per hundred cubic centimeters of blood) months after the synovectomy indicated a primary disturbance of the lipoid metabolism which led to the production of xanthoma in a joint weakened by occupational trauma or by some inflammatory factor.

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18. Kling, D. H.: Bilirubin in Effusions of the Joints: Methods of Estimation and Significance, Arch. Surg. **20**:17, 1930.

So far all the evidences are in favor of the benign character of these growths. Recurrences appear only when they are not removed entirely and then only in the synovial membrane. Early diagnosis is important in view of the continuous bleeding and growth of the lesion. The importance of early aspiration and examination of the synovial fluid is to be emphasized.

Operation should be performed as soon as the diagnosis is made and should consist of the removal of as much of the synovia as possible. In case a complete synovectomy cannot be performed it may be advisable to give deep radiation. The prognosis is favorable, but a possible recurrence must be considered. A check-up examination of our patient one year after the operation showed perfect motion of the knee joint and no recurrence of symptoms.

SUMMARY

1. Diffuse hemorrhagic villous synovitis due to xanthoma of the left knee joint was successfully treated by synovectomy. A year and a half after operation there was no recurrence of symptoms.

2. Repeated examination of the blood up to one year after operation showed a hypercholesteremia, indicating a primary disturbance of the lipoid metabolism as the underlying cause for the precipitation of lipoids and the formation of the xanthoma.

3. A critical review of the reports of cases and the theories of pathogenesis of this rare condition is given.

4. The complete removal of the growth promises permanent cure. Early diagnosis is therefore of paramount importance and can be accomplished by careful examination of the joint fluid, and especially by the estimation of the bilirubin and cholesterol content of the effusion.

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CONGENITAL COXA VARA

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INTRODUCTION AND REVIEW OF THE LITERATURE

The words varus and valgus, it seems, originally had an identical meaning signifying steep or oblique. Later a differentiation was introduced, so that varus now means a deformity in which the extremity distal to it bends toward the midline. Valgus has the opposite significance.

Isolated reports of coxa vara appear in the literature prior to the description given by Fiorani in 1881 of a group of fifteen patients whose disability he concluded was due to a change in the angle of the neck of the femur. It is difficult to judge in the present light just what cases were included, as he specifically stated that motion at the hips was normal in many of these cases. He mentioned the fact that several of the patients were children of consanguineous marriages. He suggested that improper food may have a bearing, which suggests that some of the cases may have been of rachitic origin. He described a typical caliper brace for support, which even included a ring at the top with a joint at the knee. One will appraise this report at its true value if one realizes that it appeared in 1881, some years prior to the discovery and use of roentgen rays.

In 1888 Müller again called the attention of the surgical world to a deformity of the femoral neck, with adduction of the distal part of the limb, which depressed the neck of the femur from the usual 125 to 130 degrees. The cases described were apparently instances of epiphyseal separation at the hip.

The name "coxa vara" was given by Hofmeister in 1894, and this appellation took root immediately. As I understand coxa vara, it is a depression of the neck of the femur, so that the angle which the neck of the femur makes with the shaft is less than the normal angle of 125 or 130 degrees seen in adults. Hence it approaches 90 degrees, or it may be less than 90 degrees. The deformity may be at the base of the neck, or nearer the head of the femur. One must realize also that the neck of the femur may not be in the same plane that passes through the condyles of the femur. Normally there is some anteversion of the neck of the femur, which may amount to as much as 20 degrees, according to Elmslie. In coxa vara, the neck of the femur may be depressed directly downward, or the greater trochanter may, with the base of the neck, be forward or backward.

Congenital coxa vara is obviously the most infrequent type. The literature on it, however, is more extensive than one would expect.

Congenital coxa vara was described by Kredel in 1896. In his cases and the cases described by earlier authors, there were other malformations, such as knock-knee, equinovarus or a defect of the patella. In Kredel's original report there were two cases, one in a child, aged 5 months, and the other in a child, aged 3 years. Attention was attracted to the first case by the peculiar position assumed. One hip was held in adduction and the other in abduction. This suggested to the author a lack of space in utero as a possible etiologic factor. The second child could not stand or walk. It is of interest that the author mentioned a limitation of abduction at the hip in these cases and considered it a point of differentiation from rachitic coxa vara. This one knows is not true. Coxa vara due to rickets shows the mechanical limitation of abduction.

Kirmisson, in 1897, reported the autopsies made on two infants, aged 2½ and 1 month, respectively. These included the hip joints, which showed what he considered to be congenital coxa vara. He found the greater trochanters to be much posterior and stated that this was due to the short posterior fibers of the capsule.

Mouchet and Aubion, in 1899, called attention to the fact that congenital coxa vara is not necessarily associated with other congenital anomalies. (Apparently the only cases recognized earlier were observed on examination incidental to the finding of the other obvious deformities.) These authors stated specifically that their cases of congenital coxa vara showed no signs of rickets.

Alsberg, in 1899, observed congenital dislocation of the hip on one side and congenital coxa vara on the other. He was the first to suggest that intra-uterine pressure may have been sufficient to cause a dislocation of the hip on one side and only enough to depress the neck of the femur on the other.

Reiner, in 1903, recognized congenital coxa vara as one stage of a rather extensive femoral defect and first suggested a theory as to its causation.

Hoffa, in 1905, described a case of bilateral congenital coxa vara in a boy, aged 4 years. A resection of both hips was performed in 1902. Hoffa considered that the developmental disturbance of the normal epiphysis was the cause of the deformity. A microscopic examination of the specimen was made, which will be referred to later. This is the first microscopic report of congenital coxa vara. Others have been made by Delitala and Barr. A specimen was removed by Nilsonne, who stated that a microscopic report (1928) would be made later. No record of this report could be found. In the discussion of Nilsonne's report Camitz stated that four specimens were removed by him.

Hoffa suggested that a differentiation between rachitic and congenital coxa vara might be made on the direction of the epiphyseal line in the neck of the femur, as seen in the roentgen film, which he stated is vertical in congenital coxa vara and oblique in rickets, being oblique from above and outward, downward and inward.

Feiss, in 1906, reported a case of congenital coxa vara in a girl, aged 3 years. This was of the type originally described by Kredel. Here, dating from birth, the left lower extremity was held adducted into approximation with the right. Feiss quoted from Kredel, "When one has seen this well nourished and active child taking this position repeatedly, then one cannot doubt the fact that both legs had grown in this position in utero for a long period."

Francke, in 1906, reported congenital coxa vara in siblings. They were a boy, aged 6 years, and his two sisters, aged 5 and 2 years respectively.

Helbing, in 1906, suggested that congenital coxa vara is manifested in delayed or deficient ossification of the upper end of the femur.

Ghuilamila, in 1907, reported a case of congenital coxa vara (bilateral) complicated by tuberculosis on one side. This diagnosis of tuberculosis was based on clinical and roentgen findings.

Frisch, in 1908, reported a case of bilateral congenital coxa vara in a girl, 7 years of age. He stated that up to that time about thirty cases had been described in the literature.

Rafilsohn, in 1908, reported two cases of congenital coxa vara and stated that congenital dislocation of the hip had been observed on one side and congenital coxa vara on the other.

Spitzy, in 1909, stated that there was no causal connection between congenital coxa vara and congenital luxations, but that coxa vara associated with a luxation is, as a rule, of secondary origin.

Drehmann reported a case of congenital coxa vara in a girl of 16, in whom he reported raising the angle of the neck of the femur to 120 degrees from 65 degrees by stretching the hip into full abduction. The defective portion of the neck gave way under tension, permitting the correction. A plaster of paris spica was left on for five months. Later a fixed abduction deformity was corrected by a simple osteotomy; Drehmann stated that the functional result was highly satisfactory.

Mayer, in 1910, reported a case of bilateral congenital coxa vara in a twin, aged 24. The patient showed a greater angle of the neck of the femur on the right side than on the left. The complaint of disability was greater on the right side. Mayer called attention to the fact that the disability was due to extra-articular strain on the capsule, muscles and the like. Owing to atrophy of the neck of the femur, Mayer stated, the head of the femur looked like a mushroom or like the head of a giant placed on the neck of a dwarf.

Delitala, in 1913, reported a case of congenital coxa vara of the left side in a child of 3 years on whom a subtrochanteric osteotomy had been performed. One month after the operation the child died of pneumonia. At postmortem examination the muscles, capsule and ligaments of the hip were found to be normal. Histologic examination of the head and neck of the femur was made.

Schwarz, in 1913, reported three cases of congenital coxa vara. In each case the patient began to walk at about 15 months of age. In one patient observed at the age of 4 years there was a defect in the neck of the femur with the commonly seen area of transparency shown in the roentgen films. Eleven years later the defect had spontaneously disappeared, and in its place there was well developed bony tissue.

Elmslie, in 1913, in reviewing coxa vara in general designated congenital coxa vara under the title of infantile coxa vara. He described a gross specimen which had been removed by Robert Jones from a woman, aged 26, and another which he found in the museum of St. Bartholomew's Hospital. The hips from both patients were preserved. The defects were accidentally discovered in the dissecting room.

Following Elmslie's designation of infantile coxa vara, Perrier, in 1914, reported a case of congenital coxa vara observed by Nove-Josserand at autopsy in an infant dead at birth. Congenital coxa vara and dislocation of the hip were coexistent.

Brand, in 1916, mentioned the important fact that the prognosis in congenital coxa vara is entirely dependent on whether or not ossification occurs in the defect in the neck of the femur. Failure of union to materialize fully predisposes the patients to a fracture of the neck of the femur in later life, with resulting nonunion and pseudarthrosis and with the marked displacement and absorption of the useless femoral head involving serious disability.

Lepoutre, in 1921, reported a case of right-sided congenital coxa vara with absence of the patella on this side. The child was 6½ years old. Lepoutre expressed his belief in an unjustifiably hopeless outlook.

Nilsonne, in 1924, suggested that the anomaly of ossification may be basically due to an embryonic vascular disorder. In 1928 he reported bilateral congenital coxa vara in a girl of 7 years, who died of tuberculous meningitis. He stated that there was defective ossification with an irregular epiphyseal line, and that several islands of cartilage were found in the epiphysis and the metaphysis.

In the discussion Camitz stated that he removed four femoral heads from patients with congenital coxa vara and examined them histologically. No epiphysis was found. Cartilage of different kinds and islands of bone and connective tissue were lying about in profusion.

Noble and Hauser, in 1926, published an excellent review of coxa vara in general, including also the congenital type. They stated that operations on the necks of the femurs in the congenital type were frequently disastrous, and that nonunion might ensue. They presented roentgen films of a man with congenital coxa vara and nonunion of the neck of the femur and also showed the roentgen appearance ten years previously with a typical attenuated neck.

Fairbank, in 1927, reported a case of congenital coxa vara and showed a roentgen film. There appeared to be no neck. (It was supposed that the neck was present but unossified.) The child was 3½ years of age. There was a shortening of 4½ inches on the affected side. Practically all of the shortening was in the femur. It was proposed that an osteotomy be done later to correct the deformity. The child died suddenly at operation. Death was due to massive pulmonary thrombosis. The specimen showed that the defect in the neck of the femur was nonexistent. In this location there was cartilaginous tissue.

Fairbank presented a rather complete review of the subject in 1928.

Peabody, in 1927, reported in full a case of typical congenital coxa vara (bilateral) in a woman, aged 23.

Jansen, in 1929, suggested that pressure in utero on the flexed knee in the axis of the femur may have a bearing on congenital coxa vara (coxa fracta).

Barr, in 1929, reported five cases of congenital coxa vara with a histologic report of a specimen removed from one of the patients. The other patients were not operated on.

Kreuz, in 1930, discussed congenital coxa vara and reported the case of a child whose roentgen findings presented an epiphyseal line in the neck of the femur that at first was vertical, but which three years later was slanted. He therefore felt that this disproved Hoffa's suggestion that the epiphyseal line is vertical in the congenital form of coxa vara in contradistinction to the other forms.

Bargellini reported a case of bilateral congenital coxa vara followed clinically and roentgenologically for a period of twelve years. The child was seen from the age of 4 years to the age of 16. The deformity was marked on one side. On the other side it was mild. On the more markedly involved side it progressed to separation of the epiphysis. On the less marked side there was healing with anatomic and functional cure under conservative treatment. The more involved side, on which the condition progressed to nonunion, was operated on at the age of 16.

Sacerdote, in 1931, showed a girl, aged 4½ years, with congenital dislocation of the right hip and congenital coxa vara of the left hip of 90 degrees. This was confirmed by roentgen findings. The right hip was easily reduced under anesthesia. Six months later a subtrochanteric

osteotomy of the left hip was performed. Nine months after operation a normal osseous structure of the head and neck was found, with the angle of the neck at 120 degrees. The epiphyseal line had practically disappeared.

ETIOLOGY

As in other congenital anomalies, any suggestions as to the cause of coxa vara that one finds at birth are purely theoretical.

Alsberg, in 1899, suggested that intra-uterine pressure may account for the congenital coxa vara.

Helbing felt that there was perhaps a fissure with a lack of proper ossification in the neck of the femur. He felt that there may be an abnormal anlage which came to expression in postfetal life.

Reiner also suggested intra-uterine pressure as having an important bearing on the condition. He stated that at about the tenth week of fetal life the normally abducted and flexed femur becomes adducted, and at this time an angle is formed between the neck and the shaft of the femur. Pressure of the membranes may cause a complete obliteration of the bone at the hip. Less pressure may cause only congenital coxa vara.

Hoffa made almost the same suggestion, that because of intra-uterine pressure the neck of the femur loses its property of growth.

Drehmann followed out much the same idea and considered the abnormal zone in the neck of the femur simply a defect of the first degree. A more marked defect may indicate the absence of a variable portion of the upper portion of the femur.

Nilsonne, in 1924, suggested that the anomaly of the neck of the femur may be due to an embryonic vascular disturbance.

MICROSCOPIC APPEARANCE

The microscopic appearance of bone removed from the affected portion of the neck of the femur shows nothing characteristic.

The description of a gross specimen was given by Elmslie:

> The specimen resected by Mr. Robert Jones from a woman, aged 26 years, in whom both hips were affected, and whose symptoms dated from birth, shows very well the condition finally attained (Royal College of Surgeons Museum, Specimens 1785d and e). The head of the bone is displaced downward, so that only a narrow interval remains between it and the shaft, the neck pointing downward and inward. The lower part of the head, neck and shaft are continuous, with, however, a fine fibrous intersection between them; above this a clear line of fibrous tissue separates the head and the adjacent part of the neck on the inner side from the root of the neck on the outer, a separated area of bone of a different texture, and a space containing fibrous tissue existing here also. The Museum catalogue says: "The appearances, therefore, indicate that a solution of continuity has taken place between the neck and the head close behind the latter,

that osseous union has followed between the opposed lower portion of the neck and the head (?), and that a formation of callus has occurred upon the exposed surface of the neck and occupies the interval between this and the higher part of the head."

This was evidently a case of congenital coxa vara which had progressed to nonunion of the neck of the femur.

Elmslie reported another gross specimen which he found in the museum of St. Bartholomew's Hospital.

Nilsonne published the description of a gross specimen from a child, aged 7 years, who died of tuberculous meningitis.

Neither of these cases was accompanied by a report of a microscopic examination.

Hoffa reported that:

A section including the entire width of the head and neck of the femur and part of the adjacent femur itself was microscopically examined. The cartilaginous portion of the specimen consisted almost throughout of permanent cartilage, which was highly vascularized in several spots. Among the sanguineous capillaries there was very loose connective tissue with small foci of extravasation. Near these vascular islands the basic cartilaginous substance was more fibrous. There was nowhere any indication of proliferating cartilage. Near the center of ossification of the head of the femur there were irregular nodules of cartilage, whose capsules stained deeply with hematoxylin and showed granular calcification. This zone showed no indication of cartilaginous proliferation. The nodules showed occasionally a few isolated spicules of bone. At the periphery of the nodules the cartilage was transformed into fibrous connective tissue. Nearer the center of ossification the fibrous transformation of the cartilage was more extensive. At a small circumscribed spot the cartilage was necrotic and invaded from all sides by very cellular connective tissue. The periphery of the cellular layer adjacent to the necrotic cartilage showed also isolated, rounded and multinuclear giant cells. The spicules of bone were extraordinarily irregular. They showed absolutely no conical arrangement in the direction of the cartilage. Only a very few and isolated spots showed a border of uniformly directed cells interpreted as osteoblasts. The medullary spaces had very few cells and abundant fat. Vascularization was poor. Occasionally the marrow was transformed into fibrous connective tissue with few cells. The periosteum also showed no cell proliferation or transformation into bone spicules.

The report by Delitala in 1913 follows:

Histologic Examination.—For the histologic examination I employed a slice taken from the centre, including the whole section decalcified by Schafer's method, and stained with haematoxylineosin, with carmin, and Schmorl's method number two. For the sake of clarity I shall divide the description into three parts: (1) the part concerning subtrochanteric osteotomy and the line of the callus; (2) the part dealing with the neck of the femur together with its bony part, its conjugate cartilage, and the zone of ossification which lies between; (3) the part that refers to the head of the femur and that is the least interesting.

As regards the osteotomy, we find that the corticals of the diaphysis incuneata and of the two trochanters are joined together by abundant bone trabeculae run-

ning obliquely and circumscribing areas of medullary tissue of the fibrous type; the ossification of the callus has proceeded according to the normal type in man and in such a way as to secure good union between the stumps.

In the neck of the femur we find an anomalous spongy tissue.

In the bone marrow of the femoral neck we do not find the typical young tissue corresponding with the age, but a marrow with numerous adipose elements and with extensive haemorrhages. Furthermore, it is not rare for it to contain cartilaginous nodules which, because they are of the same type as the conjugate cartilage, must be interpreted as the latter's remains not ossified and dislodged by the formation of the surrounding laminae of bone.

The cartilage of growth is formed by a hyaline (tissue) of very small cells, where the zone of repair is more extensive than any other: the region of proliferation shows capsules containing two, three, and more nuclei, but here, too, as opposed to what normally happens, the daughter cells stay small and have an oval nucleus which is very regular and stained heavily and homogeneously: at the edge of the diaphysis there is a thin and noncontinuous layer of cartilage with columns, but with elements of the same type, without any sign of decomposition of the cartilaginous cells; and the fundamental substance does not show that impregnation of calcium salts which is revealed in the region of normal ossification.

But still more notable is the fact that in its midst there are serpiginous, invading vascular areas where a capillary with numerous lateral buds is surrounded by a dense connective tissue, soft and spindleshaped; the presence of the areas cannot be attributed to the oblique direction of the section. The finding is comparable with the figure which Axausen gives of the vascular resorption of the cartilage in articular transplants. In some sections it is possible to follow one of these vasal plugs which excavates a canal from the diaphyseal surface of the conjugate cartilage up to the epiphyseal surface and thus connects the medulla of the nucleus of the head with that of the neck, yet without the slightest sign of formation of bone substance along its margins, either.

As for the zone of ossification, in addition to the zone already mentioned in regard to the stratum of the cartilage with columns which is deep down and at rest, because the capsules are not broken, its cells do not recede, its substance is not calcified, the irregularity of the course must be noted: instead of constituting a line that is almost regularly rectilinear and oblique with respect to the horizon, perpendicular with respect to the axis of the neck, it forms an almost horizontal streak shaped like a wreath.

Along it the endochondral ossifications take place slowly and are not continuous: after stretches in which slender trabeculae of bone are seen outlined along the cartilage in series come others in which the medulla approaches the cartilage without giving any signs of activity.

This finding explains to us the reason for the presence of cartilaginous nodules right in the ossified zone. The active zones, advancing just behind the inert ones, end by leaving the latter heterotopic, so that it is not necessary to resort to occurrences of metaplasia or something else to explain them.

What must be considered as the principal fact shown by the histologic finding, it seems to me, is the anomalous constitution of the conjugate cartilage, with which are connected the altered direction of the line of ossification, the slowness of the bone transformation, and the irregularity of form and arrangement of the spongy trabeculae: they are all facts which together account for the deformity of the neck of the femur and which I shall call dystrophic.

Barr reported the microscopic appearance of a specimen from one of his cases:

Six sections were made of the fragment of tissue received, which were composed of bone cartilage, fibrous tissue and muscle. Portions of the bony fragments showed the usual bone spicules and bone marrow. In three sections there was an alteration in the histology from that found in normal bone. The cartilaginous junction with the bone spicules was rather abrupt. The cartilage cells did not assume the linear arrangement nor the enlargement usually found along the line of ossification. The invasion of cartilage by blood capillaries was entirely absent. The marrow space in these sections ended abruptly at its junction with the cartilage. Cartilage was similar in appearance to that found in the articular surface. The cartilage in one area was found to be intimately united with bone spicules rather deep in the spongy bone. Islands of disintegrated cartilage were also found between the bone spicules. Some of the spicules showed evidence of faulty laying down of bone matrix and some atrophy of bone. Nowhere was there marked evidence of bone formation, nor was there evidence of repair. Owing to the fragmentary character of the tissue, the exact relation of this cartilage to the surrounding bone could not be determined. The histology was not sufficiently characteristic to permit a definite diagnosis as to the cause of the bone change. Somewhat similar changes are sometimes found in bones of animals in which there is a vitamin deficiency, other than those which are known to influence the laying down of normal bone.

The report, by Dr. H. L. Jaffe, pathologist at the Hospital for Joint Diseases, of a segment removed by me from the superior border of the neck of the femur of a patient, aged 5 years, follows. The segment included a portion of the articular cartilage and neck of the femur down to the greater trochanter.

Section of the larger piece, which revealed the articular cartilage, showed degenerative phenomena in the deeper layers of the cartilage with areas suggestive of mucinous degeneration and also the appearance of tiny intracartilaginous cysts, apparently on the basis of liquefaction of the cartilage. The subchondral bone was compact, there being widespread subchondral osteosclerosis, which extended through the entire capital epiphysis from the area from which the section was taken. Between the thick trabeculae there was a rather loose connective tissue containing vessels, osteoblasts on the surfaces of the canals and, in places, osteoclasts. Between the thick trabeculae areas of marrow were observed; in some regions the marrow showed an increase in the connective tissue stroma and also slight evidence in places of connective tissue bone formation. What was observed of the epiphyseal cartilage plate was extremely difficult to interpret, since it was at the edge of the section, the surgical specimen apparently passing through areas of the plate. The epiphyseal cartilage plate showed changes which might be interpreted as evidence of beginning closure. These changes extended down toward the neck, where the bone was sclerotic. An occasional islet of included epiphyseal cartilage plate was observed within the substance of the bone. Another fragment of bone, apparently from the neck, showed considerable compact sclerotic bone with fragments of the epiphyseal plate and other fragments of epiphyseal cartilage plate within the substance of the epiphysis.

Specimens of the defective portion of the neck of the femur from three other cases of congenital coxa vara have been removed and examined at the Hospital for Joint Diseases. They are referred to in the individual case reports.

HISTORY AND PHYSICAL FINDINGS; DIFFERENTIAL DIAGNOSIS

The deformity and painless limp are the striking signs in these cases in childhood.

Pain begins in adolescence or adult life if the patient is not treated; if the neck has given way with resulting nonunion, the disability is marked, so that the patient seeks relief.

Examination shows all of the cardinal signs of coxa vara: a limp; elevation of the greater trochanter; limitation of abduction; sometimes

Fig. 1.—Photomicrograph showing microscopic cyst in the articular cartilage.

internal rotation; more rarely, external rotation; a positive Trendelenburg sign, and the head of the femur palpable beneath the femoral artery in the groin. If the condition is bilateral, a markedly increased lumbar lordosis is present.

In contrast to the cases reported in the early literature in which other congenital anomalies were associated, the cases which I am here reporting showed no other anomalies.

The children begin to walk tardily, as a rule about the fifteenth month or later, and it is then that a peculiar gait is observed. The history is not characteristic, and it could be readily confused with congenital dislocation of the hip. The gait may not make sufficient impression on the parents at this early date, and several years may intervene before the child is brought for medical attention, though the

majority of cases at the present time, owing to better education of the masses by medical men, are seen early.

There may be a history of injury, but more careful questioning will disclose the fact that the condition antedated the injury, and that the injury was not severe enough to have initiated the condition. The added disability after the injury is likely to be transient, though it may suffice to focus attention locally.

If the condition is bilateral, the increase in the lumbar lordosis is more striking, and the resemblance to congenital dislocation of the hip is more striking, especially with the presence of a waddling gait.

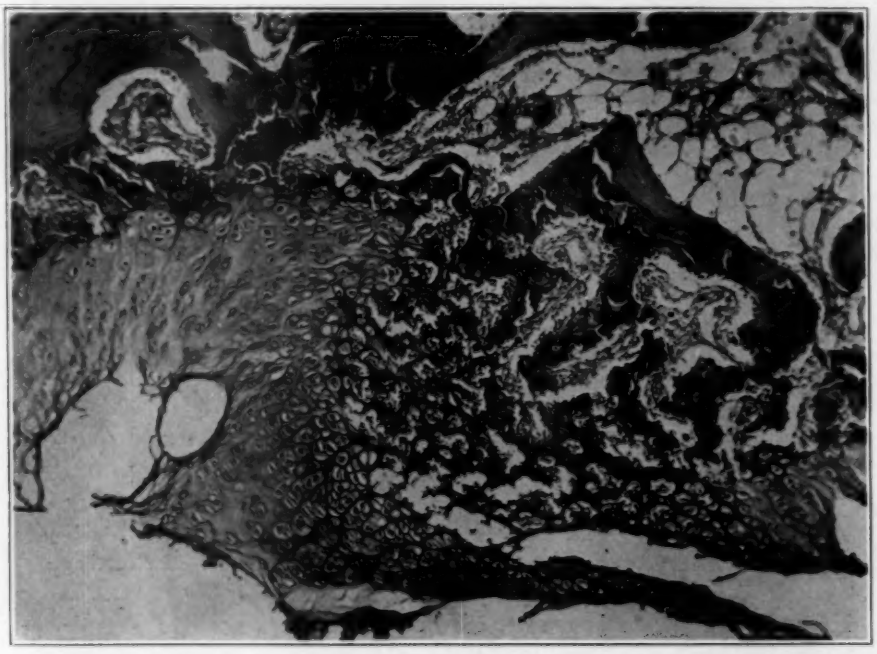

Fig. 2.—Photomicrograph showing the irregular distribution of the cartilage cells in the epiphysis.

On physical examination the greater trochanter is found to be elevated and prominent. The greater trochanter is apparently usually posterior to its common position, and there may be a fixed flexion deformity at the hip in the older cases. In contrast to congenital dislocation of the hip, the head of the femur is found in a more or less normal position with relation to Poupart's ligament, and when force is applied in the axis of the femur and relaxed alternately, the hip does not "pump" or "telescope." Because of the lack of proper balance at the hip, Trendelenburg's sign is present, and even after correction of the depression of the neck of the femur, with restoration to nearly normal,

this sign may remain positive. This is no doubt influenced by a shortened neck, whether or not it is the result of operative intervention.

Unless there are secondary changes about the hip joint, influenced by the development of a superimposed arthritis, there is no muscle spasm or other evidence of an acute condition. There is no local sensitiveness.

There is limitation of motion, but this limitation of motion is, without secondary changes, entirely mechanical. One therefore expects limitation of abduction, and this may be slight or great, depending on the degree of depression of the neck of the femur and its impingement

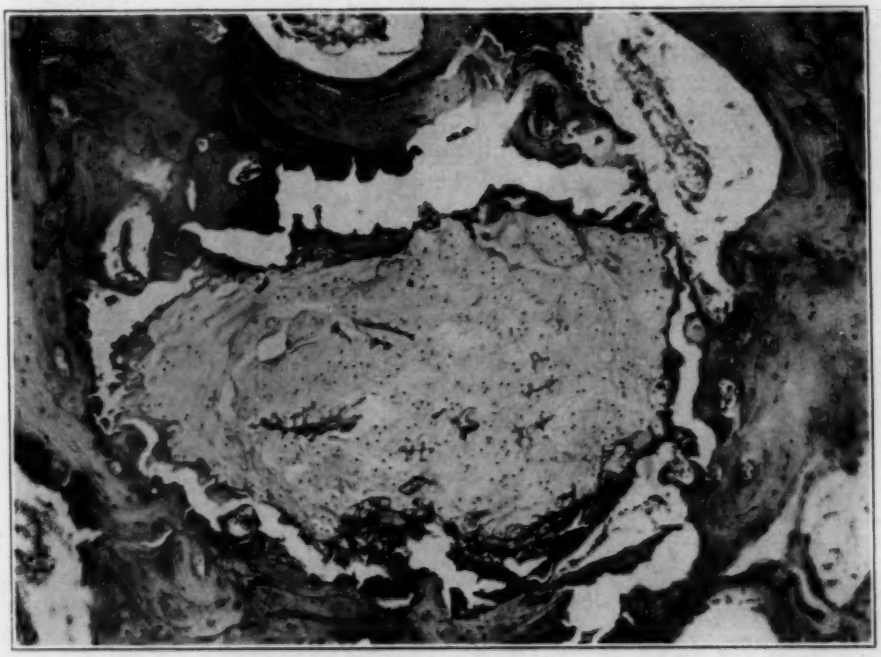

Fig. 3.—Photomicrograph showing an island of cartilage surrounded by bone. In areas the surrounding bone is dense.

against the rim of the acetabulum or the striking of the greater trochanter against the side of the ilium in forced abduction. Shortening of the soft parts, particularly in the older cases, will limit motion. This is especially true of the adductor muscles of the thigh and the portions of the capsule, particularly the posterior part.

ROENTGEN APPEARANCE

The roentgen appearance of these cases is most interesting, and unless one is familiar with it, the proper diagnosis will not be made. The obvious thing is the depression of the neck of the femur. As one

looks more closely, there seems to be loss of substance in the neck, which to the uninitiated immediately suggests a fracture with resulting nonunion. The epiphyseal line in these cases, as first mentioned by Hoffa, is vertical, with a branching, usually at its inferior portion (though it may be superior) like an inverted Y enclosing bone between its two arms. This defect is much wider than the normal epiphyseal line.

(Fractures of the neck of the femur in infants and children are uncommon. They require severe trauma for their production. They are usually of the hinge type at the base of the neck and heal readily.)

The greater trochanter is elevated, and in the older cases it becomes much elongated and takes on a "beaked" appearance. It may be in contact with the ilium.

In the adolescent this defect in the neck of the femur may give way completely, and resulting nonunion may be truly present, with no contact between the head fragment and the contiguous portion of the neck of the femur, or there may be fibrous union. The shaft may then be displaced upward, so that the head fragment may be at the level of the lesser trochanter.

The head of the femur occupies the lower portion of the acetabulum and is often partially below the lower rim. Later it becomes more or less depressed from the acetabulum and appears to be near to, or in contact with, the lesser trochanter. In some cases of this sort the head is much larger than the attenuated neck, and no better description of the relationship can be given than that of Mayer, who said that the head was mushroom-shaped, appearing like the head of a giant on the neck of a dwarf.

The acetabulum may show considerable change in outline. It is shallow and defective in its inferior portion, owing to pressure from a relatively large head of the femur, which is low in its relationship to the acetabulum. At times shadows are seen in the acetabulum suggestive of osteochondritis.

PROGNOSIS

The prognosis is governed entirely by what happens in the neck of the femur where defective ossification is present. If the condition is mild, according to reports, ossification may proceed uninterruptedly. Unfortunately, this is not the usual happy outcome. If this were true, one would be justified in waiting for complete ossification and then correcting the coxa vara. Without surgical intervention the condition tends to become progressively worse, and in untreated patients to result in separation of the head of the femur and nonunion. At this stage there are secondary arthritic changes, with pain and great disability.

TREATMENT

The older writers held a rather hopeless and more or less helpless view of these cases. The patients were treated by forced abduction in traction or plaster of paris dressings.

The line of treatment should have two definite goals, both attained by surgical intervention.

1. The defect in the neck of the femur should be overcome by an operative opening up of a new blood supply, preferably through drilling the neck of the femur. This means obliteration of the epiphyseal line. In several of the cases reported here this was accomplished by different surgical procedures, such as the insertion of a beef-bone peg, the insertion of an autogenous peg and the removal of a disk of bone from the neck.

Operations directly on the neck in these cases are attended by more than the usual risk of infection because of the defective tissue with an inadequate blood supply. The drilling from below the greater trochanter into the neck seems to be the simplest procedure.

2. After the neck has been sufficiently ossified, a wedge osteotomy of the subtrochanteric type should be done to restore the angle of the neck of the femur.

I feel that these procedures should be carried out when the patients are first seen, that is, from about 3 years on.

A reconstruction operation, such as the Whitman or Brackett type, should be reserved for older untreated patients with nonunion. If proper operative care is given early, few, if any, reconstruction operations will be necessary.

REPORT OF CASES

CASE 1.—E. R., a white girl, aged 7 years, was breast fed for fifteen months. The family history and the patient's history were unimportant. The birth was normal. There was no history of injury. The patient walked alone at 16 months of age.

The child was brought to the Hospital for Joint Diseases in October 1927, because of a limp and shortening of the left lower extremity. When she was 3 years old, her mother noticed that she limped. She was treated in another institution by the application of a plaster of paris spica, which was worn for six months. This resulted in no improvement. The condition progressed. The patient could walk a considerable distance without fatigue. There was no history of injury to the hip.

General examination gave negative results. The patient walked with a limp on the left side. The only motion limited at the left hip was abduction, which could be carried out to 10 degrees as compared with a normal range on the right.

Measurements showed that the distance from the anterior superior spine of the ilium to the internal malleolus on the right (which will be designated as R.A. in the remaining cases) was 24¼ inches.

The distance from the anterior superior spine of the ilium to the internal malleolus on the left (which will be designated at L.A.) was 23 inches.

The distance from the umbilicus to the internal malleolus on the right (which will be designated as R.U.) was 26 inches.

The distance from the umbilicus to the internal malleolus on the left (which will be designated as L.U.) was 25 inches.

The circumference of the right thigh (which will be designated as R.T.) was 13¼ inches.

The circumference of the left thigh (which will be designated as L.T.) was 13¼ inches.

The circumference of the right calf (which will be designated as R.C.) was 10 inches.

Fig. 4 (case 1).—Showing left congenital coxa vara.

The circumference of the left calf (which will be designated as L.C.) was 9½ inches.

The Wassermann reaction was negative.

The roentgen examination on November 8 showed a normal hip on the right side. On the left there was coxa vara of 80 degrees. The head of the femur was relatively large and low in the acetabulum, being partially out of the inferior border of the acetabulum. The epiphyseal line of the neck was widened and vertical. The acetabulum was flattened.

A subtrochanteric wedge osteotomy was performed on November 9. A 5 inch incision was made over the lateral aspect of the left femur, exposing the upper part of the shaft. The tissues were stripped back until the trochanter and neck and a little of the head of the femur were exposed. The deformity of the neck was clearly demonstrated. A specimen of bone running through the neck and head was removed for microscopic examination. Then a wedge of bone, measuring

three-eights inch at its base, was removed from the intertrochanteric line. It was then possible to abduct the hip to 35 degrees. After closure of the wound a plaster of paris spica was applied in this attitude.

A microscopic examination of tissue removed from the head and neck of the femur was made by Dr. H. L. Jaffe. It showed no characteristic lesion of the bone.

The patient was readmitted to the Hospital for Joint Diseases, and the plaster of paris spica was removed on Jan. 4, 1928. The spica was bivalved, and the extremity carefully removed from it. At the site of osteotomy the bone was solid.

Fig. 5 (case 1).—Appearance after subtrochanteric wedge osteotomy of the left hip. A specimen of bone was taken from the neck of the femur at the time of operation. Roentgen examination was made through a plaster of paris spica.

The trochanter rotated with the shaft. The hip showed a range of motion of about 10 degrees in all directions.

Physical therapy was instituted, and the child was allowed to walk with crutches.

Examination on Nov. 28, 1932, showed the following: The patient was satisfied with the result of her operation. She was as active as other girls and had no pain. She was in good condition. She walked with a slight limp and had a positive Trendelenburg sign on this side. There was a slight increase in the lumbar lordosis, with slight increase in the dorsal kyphosis and forward inclina-

Fig. 6 (case 1).—Appearance five years later. The coxa vara has been corrected, and most of the neck of the femur has disappeared. There is bony union of the remaining portion of the neck with restoration of the angle of the neck.

Fig. 7 (case 1).—Appearance five years after operation. The lumbar lordosis is slightly increased.

tion of the head and neck to a moderate degree. The greater trochanters were slightly posterior to the shoulders. The general posture, however, was satisfactory. The pelvis was tilted down slightly on the left. There was no spasm of the spinal muscles. The flexibility of the spine was normal. There was no sensitiveness over any part of the spine, the sacro-iliac joints or the gluteal muscles. There was an incision over the lateral aspect of the left hip beginning at the level of the base of the greater trochanter, which showed no reaction about it. The left hip was in almost complete extension and in moderate abduction. Flexion at the hip was normal. Adduction was normal. Abduction of the left hip to 30 degrees, as compared with 45 degrees on the right, was permitted. Rotation of the left hip was

Fig. 8 (case 2).—Congenital coxa vara of the right hip.

normal. The internal rotation of the right hip seemed slightly greater than normal. The patellas were normal. There was no deformity of the feet. Measurements showed: R.A., 31¾ inches; L.A., 30¾ inches; R.U., 33½ inches; L.U., 33½ inches.

CASE 2.—H. B. was a white boy, aged 7 years. His history and that of the family were unimportant. The histories were obtained from his foster mother, who had cared for him for three years. When she took charge of him he was walking with a limp on the right side, and it was reported that there was a shortening of one-half inch. This shortening gradually increased. One year before admission it was 1 inch. The limp became more marked.

The patient was admitted to the Hospital for Joint Diseases on Sept. 17, 1929, with a shortening of the right lower extremity and a limp.

The general examination gave negative results. Orthopedic examination on admission showed that the patient was in good condition. He walked with a limp on the right side. The greater trochanter on this side was elevated and prominent. It was above Nélaton's line. There was a positive Trendelenburg sign on this side. Abduction was completely restricted. Measurements showed: R.A., 19¾ inches; L.A., 21 inches; R.U., 22¾ inches, and L.U., 24 inches. R.T., 11¼ inches; L.T., 12½ inches; R.C., 8½ inches, and L.C., 8¾ inches.

Roentgen examination on admission showed that the left hip was normal. The right hip showed a coxa vara of 75 degrees. The epiphyseal line, which was vertical, was much widened and branched in its inferior portion. The large head

Fig. 9 (case 2).—Appearance six weeks after operation (subtrochanteric osteotomy and insertion of an autogenous bone graft through the trochanter and into the head). The displacement is that of a bifurcation operation. The defective tissue in the neck of the femur has been removed, and the neck has thereby been shortened. This roentgen examination was made after removal of the plaster of paris spica applied at operation.

was subluxated inferiorly from the acetabulum. The acetabulum was somewhat irregular in its lower half and flattened.

On September 25 a cervical osteotomy and bone graft were done. A 3 inch incision was made over the adductor muscles of the right hip. These muscles were freely divided, and the muscle stumps were sutured. The wound was closed with a continuous plain stitch.

An 8 inch incision (modified Smith-Peterson incision) was made, the lower end of which curved backward, exposing the trochanter. The fibers of the capsule of the hip joint were incised longitudinally, and the neck freely exposed. Its gross appearance was normal except for the marked downward angulation and a slight amount of anteversion. With a Putti hip chisel the neck was divided transversely at the point of most marked angulation. Some difficulty was experienced in dividing the cortex on the posterior surface. After division it was possible to abduct the hip freely, but a gap remained between the fragments until the shaft was rotated internally. To maintain the shaft in this position, it was decided to insert a bone graft.

Fig. 10 (case 2).—Appearance two years after operation. The deformity has been corrected, and the head of the femur is higher in the acetabulum. Union is solid.

A 3 inch incision was made directly over the anterior surface of the tibia on the right side. A bone graft, measuring 2½ inches in length by ¼ inch in thickness, was rapidly removed with an Albee saw. A drill hole was passed from the trochanter into the neck and head, and into this the bone graft was driven, jamming the two bone surfaces against each other. The extremity was immobilized in extreme abduction, and moderate external rotation in a plaster of paris spica, extending from the axilla to the toes.

The operative incision subsequently showed a mild infection.

The report of the tissue removed from the neck of the femur was made by Dr. H. L. Jaffe, who found nothing characteristic in the microscopic picture.

Examination on June 9, 1931, showed that the patient walked with a scarcely perceptible limp on the right side. There was excellent stability of the right hip. There was a marked keloid formation over the anterior aspect of the hip. The right hip was in full extension and could be flexed to 70 degrees. Abduction of the right hip was permitted to 45 degrees and adduction to 30 degrees.

Measurements showed: R.A., 22½ inches, L.A., 23⅛ inches.

The patient was able to indulge in the activities of other boys of his age.

No recent examination has been made of the patient, as he moved to a distant city and we were unable to secure a report of his present condition.

Case 3.—V. C., a colored boy, aged 7 years, was brought to the outpatient department of the Hospital for Joint Diseases on March 7, 1932, because of a limp on both sides and hollowness of the back. Birth was nomal. The patient's

Fig. 11 (case 3).—Marked lumbar lordosis.

history and the family history were unimportant, except that the mother stated that the boy fell from a shelf above the sink in July 1931. There was some discoloration over the right hip, but the patient did not complain of pain, nor did he limp immediately afterward. He walked at the age of 14 months.

Physical examination on March 23, 1932, showed that the patient was in good general condition. He walked without assistance, but he had a distinct waddle, suggestive of a bilateral coxa vara or congenital dislocation of the hips. The back was symmetrical, but there was a marked increase in the lumbar hollow. The patient presented marked flat feet. In the supine position the lumbar hollow was practically completely gone. The chest and the upper extremities were uninvolved, except that there was slight thickening of the wrist joints.

In the right lower extremity at the hip joint flexion was complete; extension was complete; abduction was checked at an angle of about 20 degrees; adduction was entirely free; inward rotation was slightly limited, and outward rotation was

somewhat restricted. At the knee and ankle joint there was no limitation of motion. The heads of the femurs were in the acetabula.

In the left lower extremity extension and flexion were free. Abduction was limited to 10 degrees; inward rotation was slightly limited, and outward rotation was somewhat restricted. At the knee and ankle joint there was no limitation of motion. Measurements showed: R.A., 23½ inches; L.A., 23½ inches; R.T., 13 inches, and L.T., 12¾ inches. The Wassermann reaction was negative.

Roentgen examination made on admission showed a bilateral coxa vara of approximately 90 degrees on both sides. There was a marked defect in the neck of the femur on both sides with attenuation of the bony substance. This was more marked on the left side. There was upward displacement of the trochanters. The epiphyseal lines of the necks of the femurs were widened and branched at

Fig. 12 (case 3).—Bilateral congenital coxa vara.

their inferior borders. The heads of the femurs were low (subluxated), and the acetabula were irregular in outline.

On admission an operation, which consisted of the removal of a specimen from the neck of the femur and the insertion of an ivory peg through the head and reconstructed neck of the femur, was performed on the right hip.

The hip was exposed through a "U" incision, with its convexity downward. The exposure was made between the tensor fasciae femoris and the gluteus medius. The greater trochanter was chiseled free in order to lengthen the neck of the femur. The capsule was thickened; there was no excess of synovial fluid, and the neck was adherent throughout to the capsule. The ligamentum teres femoris was apparently normal. The head of the femur was dislocated from the acetabulum by the operator; it was irregular in shape in the lower half and was much larger than the contiguous portion of the neck, corresponding with its roentgen appearance. A section of bone, including the attenuated portion of the neck, was removed. This was from one-half to three-fourths inch in thickness and contained hyaline cartilage. Considerable difficulty was experienced in cutting through the inferior

posterior part of the neck. The capital epiphysis was placed on a rounded portion of the base of the neck after several drill holes had been made into the capital epiphysis. The epiphysis was fixed to the reconstructed neck by driving an ivory peg from the fovea down through the neck. So little neck remained that it was reattached practically at the base of the greater trochanter. The greater trochanter was sewed lower down on the shaft of the femur by means of chromic catgut. A plaster of paris spica was applied, extending from the upper part of the chest to the toes, with the hip in 60 degrees of abduction and full extension, with the knee slightly flexed and the foot at a right angle.

Fig. 13 (case 3).—Appearance after operation on the right hip. The bone peg holds the epiphysis in contact with the neck, after a segment has been removed through the involved portion of the neck.

Following operation pyemia with foci in the left hip, the soft parts of the right elbow and the soft parts of the left arm developed. The patient survived, but with ankylosis of the hips.

Dr. H. L. Jaffe examined the tissue removed from the neck of the femur at operation and reported nothing specific on which to make a diagnosis.

Case 4.—R. L., a white girl, aged 18 months, was brought to the Hospital for Joint Diseases because of a deformity and shortening of the left lower extremity associated with a limp on this side. She had been walking for six weeks, and the

limp had been apparent since she began to walk. She was admitted to the hospital on Nov. 13, 1929, for the correction of the deformity. The family history was unimportant. The child was premature (8 months). She was breast fed for eleven months.

The child was in good condition. She walked with a limp on the left side. The greater trochanter on the left was elevated and prominent. It was three-fourths inch above Nélaton's line. There was anterolateral bowing of the femur. The left hip could be abducted to 20 degrees and the right hip to 70 degrees. Internal rotation was limited on the left. Flexion was free on both sides. There

Fig. 14 (case 4).—There is considerable shortening of the extremity associated with a defect in the neck of the femur.

was no atrophy of the left lower extremity. Measurements showed: R.A., 13 inches, L.A., 12½ inches; R.U., 14½ inches; L.U., 13½ inches.

Roentgen examination on November 14 showed slight bowing of the femurs. There were flaring of the lower end of the femoral diaphysis and a defect in the neck of the left femur, with a coxa vara of about 100 degrees. The head of the femur was low in the acetabulum. The acetabulum was relatively normal.

The patient was operated on on November 15. A 2 inch incision was made over the lateral aspect of the left thigh just below the greater trochanter. The subcutaneous tissue was completely incised and retracted. The periosteum was opened immediately below the greater trochanter and completely separated from

the femur. A wedge of bone was taken out of the femur with its base about ¼ inch in width and pointing laterally. The femur was then abducted. After closure of the wound a plaster of paris spica was applied extending from the nipples down to the toes, with the limb in wide abduction.

Examination on Jan. 2, 1930, showed that the wound was healed by primary union. The left hip was in 30 degrees of abduction. It could be brought down to 10 degrees abduction without difficulty. Complete abduction was not limited. The head of the femur rotated with the shaft. No measurements were made because of the abducted position of the extremity.

Roentgen examination of the hips was made after removal of the plaster of paris spica. It showed the coxa vara corrected by a bifurcation operation.

Fig. 15 (case 4).—Appearance after bifurcation operation on the left hip.

The patient was brought back to the hospital because of the return of the limp. Examination on March 11, 1931, revealed that she was in good condition but walked with a limp on the left side. It was noted that there were marked anterior bowing of the shaft of the femur and apparent shortening of the limb. Flexion at the hip joint was possible to a right angle. Extension was complete. Abduction was possible to an angle of about 25 degrees; adduction was free, and extension was completely free. Measurements showed: R.A., 16¼ inches, and L.A., 15⅜ inches.

The last roentgen picture that was made showed that there was a great distortion of the upper end of the femur, particularly in the subcapital region.

The patient suffered an attack of infantile paralysis during 1931.

Examination on Nov. 23, 1932, showed that the left hip was stable. There was considerable prominence of the greater trochanter. There was no fixed flexion deformity of the hip. It could be flexed to 90 degrees. Abduction on the right

was possible to 45 degrees and on the left to 10 degrees. When the patient stood, the lumbar lordosis was increased. She had a calcaneus deformity on the left. There was just a trace of power in the muscles of the calf. The patient presented a prominent heel. There were good power in the tibialis anticus muscles and slight power in the posticus muscles. There was good power in the peronei. The patient apparently had slight difficulty in the dorsiflexion of the toes. There was good power in the gluteal muscles on both sides. Measurements showed: R.A., 19¾ inches; L.A., 18⅝ inches; R.T., 13 inches; L.T., 11½ inches; R.C., 9 inches, and L.C., 7¼ inches.

In January 1933 the patient was in the Hospital for Joint Diseases, where a Whitman astragalectomy was performed on the left side.

Case 5.—S. K., a white girl, aged 5 years, was brought to the Hospital for Joint Diseases on Aug. 24, 1932, because of a limp on the left side, associated with pain. The patient's history and the family history were without significance. The patient began to walk when she was 19 months old and did not limp. Her mother could recall no history of injury, except that the child fell about March of that year. The mother stated that the patient fell down several steps, the injury not being severe. The child remained in bed for a few days. The mother stated definitely that the child did not limp before her injury and had been losing weight since.

Examination on admission showed that the child was in good general condition. She walked with a limp on the left side. The lumbar lordosis had increased slightly. The pelvis was tilted down slightly on the left. The left buttock was flatter than the right. Examination of the spine gave negative results except for slight spasm of the spinal muscles on the right side. The patient had a positive Trendelenburg sign on the left. There was no limitation of motion in the right hip. Abduction was permitted to 70 degrees. Internal and external rotation were free. There was no paralysis of the muscles.

On the left side the greater trochanter was elevated. Flexion at the hip was free. Adduction was free, and internal and external rotation were free. Abduction was permitted to 25 degrees. There was no muscular weakness.

Measurements showed: R.A., 21⅝ inches; L.A., 20½ inches; R.U., 24 inches; L.U., 23 inches; R.T., 11⅝ inches; L.T., 11¼ inches; R.C., 8⅞ inches, and L.C., 8¾ inches. The length of the right tibia was 9½ inches. The length of the left tibia was 9½ inches. The length of the femur from the tip of the trochanter on the right to the lower end of the outer condyle was 12 inches, and on the left from the tip of the trochanter to the lower end of the outer condyle, 11⅜ inches. The hips were stable.

Roentgen examination on May 19 showed that the right hip was normal. The left hip showed a coxa vara of 100 degrees. The neck of the femur was shortened. The epiphyseal line was vertical and branched at its inferior portion. There was beginning union of the epiphysis. The head of the femur was low. The acetabulum was practically normal. The neck of the femur was relatively broad.

Operation for removal of a specimen from the head and neck of the left femur and to hasten ossification in the neck of the femur was performed on August 26. The left hip was exposed through a Smith-Peterson incision. The capsule was found to be considerably thickened. There was no excess of fluid in the hip joint. There was no loss of continuity in the neck of the femur or false motion. The appearance of the neck corresponded with the roentgen appearance. A specimen through the superior and anterior portion of the head and neck three-eighths inch in width was removed. This extended from the head of the bone, included about one-half inch of articular cartilage, and passed through the substance of the neck

Fig. 16 (case 5).—There is a slight increase in the lumbar lordosis with a tilt to the left.

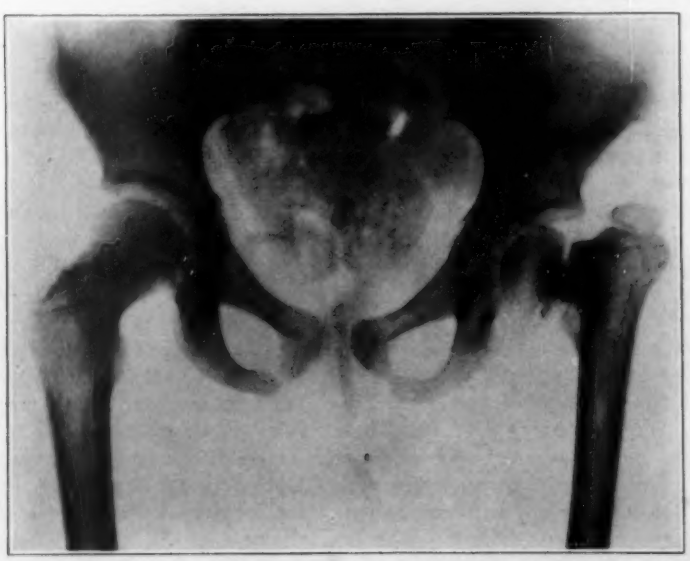

Fig. 17 (case 5).—Left congenital coxa vara. The neck is short, and bridging of bone is beginning across the defect in the neck of the femur.

and across to the intertrochanteric region, extending slightly downward toward the lesser trochanter. It was perhaps one third of the distance through the diameter of the neck. A culture was made, and the specimen was sent to the laboratory. The bone was dense and hard to cut. A small sliver of bone, which fragmented on removal, was also sent to the laboratory. The main specimen, however, was three-eighths inch in width.

A plaster of paris spica was applied, extending from the upper part of the chest to the toes, with the hip in 25 degrees of abduction, the knee slightly flexed and the foot at a right angle.

For some time after operation a swelling was noted in front of the left hip, but no suppuration ensued.

Culture made at operation gave negative results.

Examination on Jan. 2, 1933, showed that the patient was still wearing a plaster of paris spica and walking about with comfort. When union of the neck is complete, a subtrochanteric wedge osteotomy will be performed for correction of the deformity.

CASE 6.—H. C., a colored boy, aged 8 years, was admitted to the Hospital for Joint Diseases on Jan. 5, 1932. The patient's mother was mentally retarded. The history was unimportant. The birth was normal. The patient was a full-term child. He did not walk until he was 2 years old.

The child was referred to the Hospital for Joint Diseases from the school which he attended because of abnormal posture and a waddling gait. The mother noticed these abnormalities only a short time before admission, although she stated that the patient was in another institution three years before entrance because he complained of being tired and having discomfort in one hip. Traction was applied to the hip. The patient had remained in the hospital for only a few days when his mother removed him.

Examination on admission showed that the patient was in good condition. He presented extreme lumbar lordosis and walked with a waddling gait and a limp on both sides. Trendelenburg's sign was positive on both sides. The greater trochanters were elevated and prominent, being above Nélaton's line. Internal and external rotation were limited on both sides. Bony resistance could be felt on pressure anteriorly below Poupart's ligament on both sides in the position of the femoral artery. Abduction was limited to 15 degrees on both sides. There was a slight flexion contracture of the hips. The patient showed rachitic anterior bowing of the tibias.

The Wassermann reaction was negative.

Measurements showed: R.A., 22¼ inches; L.A., 22¼ inches; R.U., 23 inches; L.U., 23 inches; R.T., 11½ inches; L.T., 11 inches; R.C., 7¼ inches, and L.C., 7¼ inches.

Roentgen examination on admission showed an extreme bilateral coxa vara of 65 degrees. There was a defect in the necks of the femurs with broadened epiphyseal lines, which ran from above and inward, downward and outward. They were branched at their lower borders. The heads of the femurs were low and markedly subluxated. The acetabula were shallow but smooth in outline.

A subtrochanteric wedge osteotomy of the right hip was performed on January 14. An incision about 4 inches in length was made on the lateral aspect of the right thigh, extending from the tip of the trochanter downward on the shaft of the femur. The periosteum was stripped, and a ribbon retractor was introduced. An oblique angular osteotomy was performed, and a wedge was removed from the distal fragment, permitting the hip to be abducted to about 50 degrees without dis-

Fig. 18 (case 6).—Extreme lumbar lordosis.

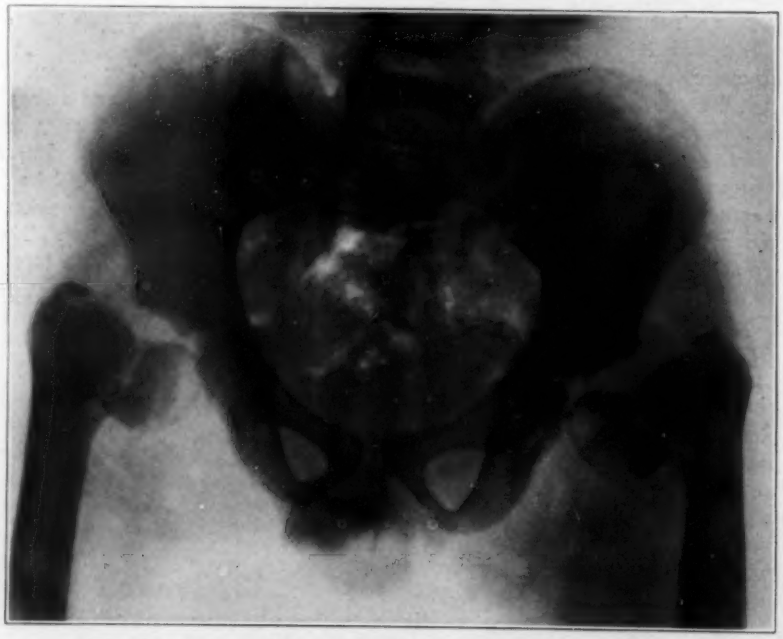

Fig. 19 (case 6).—Typical bilateral congenital coxa vara.

placement of the fragment. A plaster of paris spica was applied, extending from the line of the nipple to the toes.

Drilling of the neck of the left femur was performed on January 28. A 3 inch incision was made over the greater trochanter; the direction of the neck was thereupon palpated by passing a finger around the vastus externus muscle, and three small drill holes were made from below the greater trochanter into the neck. A plaster of paris spica was applied.

Roentgen examination of the two hips on June 3 showed that as a result of the drilling of the neck of the left femur five months before the defect in the neck of this femur had disappeared.

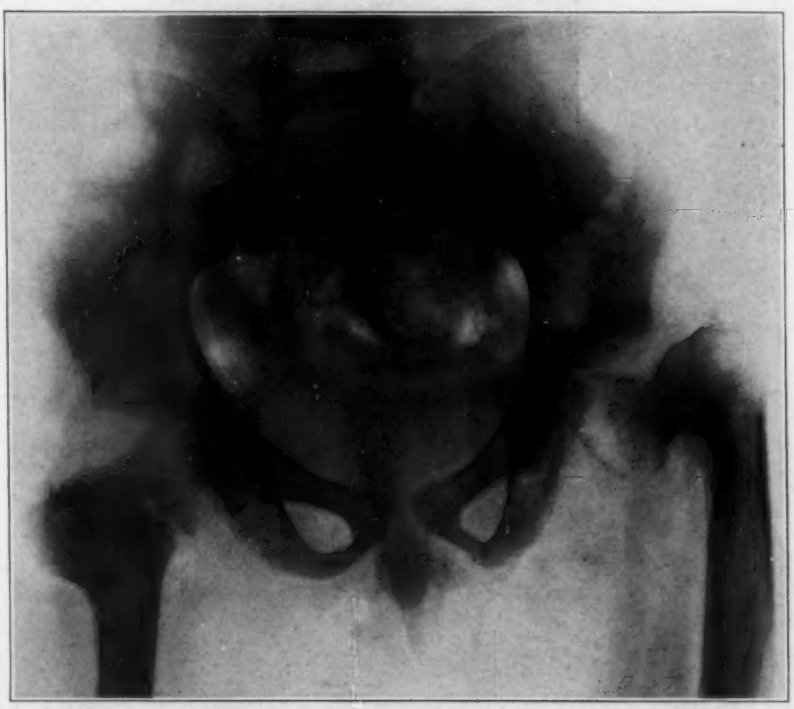

Fig. 20 (case 6).—Appearance six months after operation. There is bony union in the neck of the femur on the left side following operation by drilling. The coxa vara on the right side has been corrected by a subtrochanteric wedge osteotomy. The head of the femur on the right is now higher in the acetabulum.

A wedge osteotomy for the correction of the coxa vara is to be done later. The coxa vara on the right was corrected by operation.

CASE 7.—J. H., a colored boy, aged 10 years, was brought to the Hospital for Joint Diseases in November 1932. The patient's history and the family history were unimportant. The complaint was a limp on the left side. The child had been under the care of a stepmother. Three years before admission she had taken him to another clinic on the advice of the school nurse. The child was not treated. About a year previous to admission the limp was more noticeable. It became steadily more pronounced, but there was no discomfort at any time.

Fig. 21 (case 7).—Shortening of the left lower extremity.

Fig. 22 (case 7).—Congenital coxa vara of the left hip.

Examination on November 4 showed that the patient was in good condition. He walked with a limp on the left side. The greater trochanter on the left was elevated and prominent. There was a positive Trendelenburg sign on this side. Abduction of the left hip was limited at 5 degrees. Adduction was free. Internal rotation was slightly limited. The head of the femur was in the position of the acetabulum. Measurements showed: R.A., 26½ inches, and L.A., 25¾ inches.

Roentgen examination on November 3 showed a coxa vara of 80 degrees on the left. The head of the left femur was large. The neck was attenuated. The epiphyseal line ran from above and inward, downward and outward. It was

Fig. 23 (case 7).—Appearance after a subtrochanteric wedge osteotomy. A drill is inserted into the base of the neck and used as a handle in maintaining the position while the deformity is being corrected.

broadened and branched superiorly. The head of the femur was subluxated downward.

Operation was performed on November 16 on the Albee table, with the limb under traction. The greater trochanter was exposed through a 4 inch incision. A large Steinman nail was driven through the greater trochanter into the neck. A wedge osteotomy with the base laterally, measuring about 1 inch, was then removed from just below the greater trochanter, the apex of the wedge being at the lesser trochanter. It was then found, by gentle abduction, that it was easy to

approximate the two fragments. The wound was closed in this position, and a plaster of paris spica was applied from the nipple line down to the toes on the left side and just above the knee on the right.

Roentgen examination made through the plaster of paris spica on December 1 showed that the coxa vara was corrected by the subtrochanteric wedge osteotomy. There was a drill in the neck of the femur used as a handle at the time of operation.

Examination in January 1933 showed that the patient was still wearing the plaster of paris spica.

The neck of the femur in this patient should be drilled so that the epiphyseal line will become ossified.

CASE 8.—A. J., a white girl, aged 15, was first seen at the Hospital for Joint Diseases in July 1926.

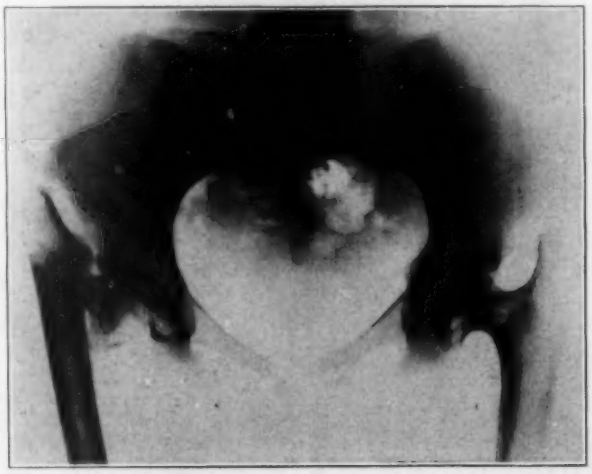

Fig. 24 (case 8).—Bilateral congenital coxa vara. There is complete nonunion of the neck of the femur on the right.

The patient's history and the family history were unimportant. The complaints were bilateral limp and pain in the right hip.

The patient began to walk late; the exact age was unknown. She had limped since she began to walk. For a long time the right hip had pained her after any unusual strain. She had recently made a misstep, and her right foot slipped (she did not fall). The pain in the right hip was acute. Since then the pain had become more marked. After sitting for a while she had great difficulty in starting to walk again.

Examination on July 12 showed that the patient was in good condition. The lumbar lordosis had increased. There was a bilateral limp which was extreme on the right, with instability of the right hip. The greater trochanters were elevated and prominent on both sides, especially on the right. There was apparent shortening of the right lower extremity of about 1 inch. The right hip was flexed to 120 degrees and was in 15 degrees of adduction. The left hip could be abducted to 15 degrees. Flexion was permitted to 90 degrees on both sides. No abduction

was permitted on the right side. The patient had a positive bilateral Trendelenburg sign. Measurements showed: R.A., 28¾ inches; L.A., 29 inches; R.U., 30½ inches; L.U., 31¾ inches; R.T., 16½ inches; L.T., 19 inches; R.C., 12½ inches, and L.C., 12⅞ inches.

Roentgen examination showed a bilateral coxa vara of 90 degrees on the left and nonunion on the right, with prominent beaked greater trochanters, an attenuated neck of the femur on the left and an ununited fracture of the neck on the right. Both acetabula were irregular in outline. This was more marked on the right side. The heads were subluxated from the acetabula inferiorly. There was almost complete absorption of the neck of the femur on the right. The acetabula

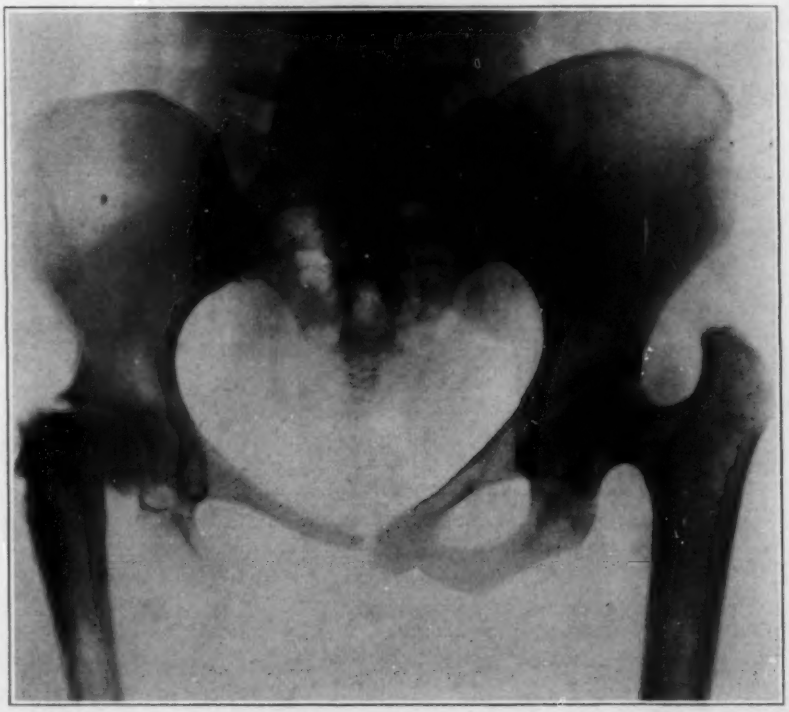

Fig. 25 (case 8).—Appearance six years after performance of a Whitman reconstruction operation on the right hip.

were shallow. The greater trochanter on the right was displaced upward to a marked degree.

The patient was operated on on July 29, a Whitman reconstruction operation being performed. A large U-shaped incision, with the convexity downward, was made on the lateral aspect of the thigh, and the fascia was cut in the same line. The muscles attached to the greater trochanter were isolated, and the greater trochanter osteotomized and reflected upward. The capsule was then opened, and the head of the femur was removed. There was nonunion of the neck of the femur. The reconstructed neck was placed in the acetabulum. A large portion of the greater trochanter was removed. (This was osteotomized earlier in the operation.) The capsule was closed, and the remaining portion of the trochanter

sutured to the femur lower down. A plaster of paris spica was applied, including the toes, with the hip in 30 degrees of abduction and slight flexion, the knee in slight flexion and the foot at a right angle.

On examination on Nov. 23, 1932, the patient appeared to be in excellent condition. She was somewhat overweight. She walked without assistance but with a marked limp on the right side. The back was flat. There was no evidence of lumbar lordosis. The chest, abdomen, back and upper extremities presented no evidences of deformity.

There was apparently an enormous overdevelopment of the left thigh, due to hypertrophy of the muscles or possibly anterolateral bowing of the femur. Extension at the hip joint was normal. Flexion was possible to an angle of 80 degrees. Abduction was limited to an angle of 5 degrees. Outward rotation was almost

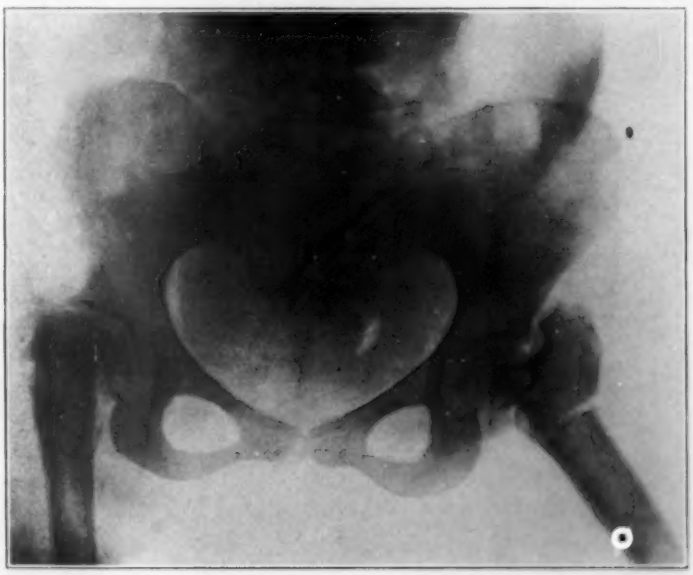

Fig. 26 (case 8).—Appearance six years after a reconstruction operation on the right hip and six weeks after wedge osteotomy on the left hip with removal of the prominent portion of the greater trochanter. Roentgen examination was made between changes of plaster of paris spicas.

free. Inward rotation was markedly restricted. Pressure over the greater trochanter was somewhat uncomfortable. Pressure over the front and back of the hip was not painful. There was a slight degree of hyperextension at the knee joint with a suggestion of knock knee.

There was, similarly, overdevelopment of the right thigh. A U-shaped scar, the result of a reconstruction operation performed six years previously, was seen. Extension at the hip joint was free. Flexion was limited to an angle of 160 degrees. Abduction was possible to an angle of about 10 degrees. Inward rotation was entirely limited. Outward rotation was markedly restricted. There was slight hypertrophy of the knee joint. Manipulation of the limb was not painful. Measurements showed: R.A., 29 inches; L.A., 29½ inches; R.T., 21⅜ inches; L.T., 23½ inches.

On November 25 a subtrochanteric wedge osteotomy of the left hip was performed, and the prominent portion of the greater trochanter (the superfluous part) was excised.

On Jan. 15, 1933, the patient was still wearing a plaster of paris spica on the left side.

CASE 9.—T. P., a white woman, aged 23, was last examined at the Hospital for Joint diseases on Jan. 20, 1933. The complaints were a limp on both sides and pain in the right hip.

The patient stated that she has three brothers and four sisters, all of whom were taller than she. She said that she did not know at what age she began to

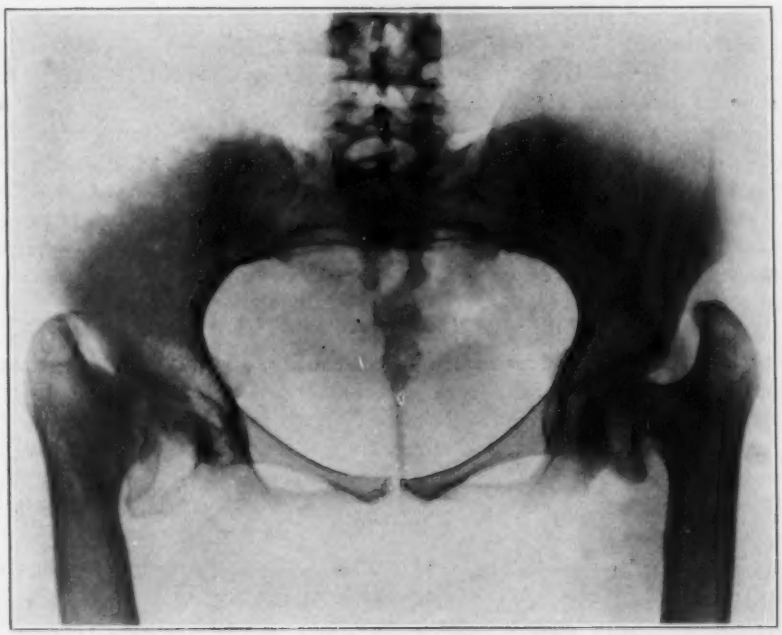

Fig. 27 (case 9).—Bilateral congenital coxa vara with nonunion of the right hip. The distal portion of the neck of the femur has not risen above the acetabulum because of a heavy fibrous union with interlocking of the fragments.

walk, but that she had limped as long as she could remember. Following a fall down a stone stairway three years before, her disability and limp on the right side had increased. She was not completely disabled at this time but remained in bed off and on for a period of two weeks.

Examination on admission showed that when the patient stood the pelvis was level. The right posterior superior iliac spine was half an inch lower than the left. The knees were in contact. There was no lateral inclination of the trunk. The lumbar lordosis was slightly increased. The posture was only fair. There was forward inclination of the head and neck. The patient walked with a limp on both sides and presented a bilateral positive Trendelenburg sign. There was no spasm of the spinal muscles. The spine was flexible. There was slight fulness

to the left in the lumbar region. The greater trochanters were elevated. The plane of the hips, as compared with the shoulders, was apparently normal. The greater trochanter on the right was considerably more elevated than that on the left. The pelvis was rather broadened. The patellas were present. There was no deformity of the feet.

As the patient lay on the table in the supine position, the lumbar lordosis was found to be increased and the right hip flexed to 160 degrees. There was no fixed flexion deformity on the left side. The right hip could be flexed to 90 degrees. The lower extremities were in slight adduction. The right hip could not be abducted. Internal and external rotation of the right hip were about one-third normal. There was sensitiveness to pressure over the anterior aspect of the right hip. The left hip could not be abducted. It could be flexed to 80 degrees. The internal and external rotations were about three-quarters normal. Hyperextension was nearly normal. Measurements showed: R.A., 27¼ inches; L.A., 27½ inches; R.U., 30½ inches; L.U., 31 inches; R.T., 16⅞ inches; L.T., 17¼ inches; R.C. 11¼ inches, and L.C., 11½ inches.

Roentgen examination on Nov. 30, 1931, showed a bilateral coxa vara of 80 degrees on the left and 45 degrees on the right. The greater trochanters were beaked and prominent. The neck of the femur on the left was attenuated, but there was bony union. The head of the femur was subluxated inferiorly from the acetabulum. It was much broader than the neck of the femur. The greater trochanter was almost in contact with the side of the pelvis. The acetabulum was small and misshapen.

The right hip showed a lack of union in the neck of the femur. The base of the neck of the femur, however, was in contact with the head fragment by a heavy fibrous union. The head of the femur was almost completely subluxated inferiorly. It was relatively large. The acetabulum was much smaller than that on the left and more irregular in outline. The greater trochanter was in contact with the ilium.

The patient is now considering having an operation on the hips, principally to give her abduction.

Case 10.—D. R., a white girl, aged 5 years, was admitted to the Hospital for Joint Diseases on Feb. 3, 1933, complaining of pain in the right hip and a right-sided limp.

The family history was unimportant. The patient was a full-term baby. Delivery was normal and noninstrumental. The patient walked at the age of 14 months.

The mother stated that three weeks before admission the child began to walk with a limp on the right side. There was no history of injury or of illness preceding the present condition except mumps one month previously, from which the patient made an uneventful recovery.

Examination on February 4 showed that the child was in good condition. She walked with a limp on the right side. The right hip was more prominent than the left. The right side of the pelvis was held slightly higher than the left. The child presented a positive Trendelenburg sign on the right side.

As the patient lay on the table the greater trochanter on the right was found to be elevated and more prominent than that on the left. The heads of the femurs could be felt in the position of the acetabula. Abduction at the right hip was permitted to 20 degrees; at the left, to 50 degrees. Internal rotation of the right

hip was about two-thirds normal. The right hip was in full extension, and flexion was not limited. Measurements showed: R.A., 20¾ inches, and L.A., 21¼ inches.

Roentgen examination on February 3 showed a congenital coxa vara of the right hip of 90 degrees. The epiphyseal line was vertical and branched at its inferior pole. The head of the femur was low in the acetabulum.

The child was operated on on February 6. A lateral incision was made, beginning at the greater trochanter and extending down the shaft. Several drill holes were made through the upper portion of the shaft, extending into the neck of the femur through the epiphyseal line. The deeper tissues were closed with catgut, and the skin with silk; soft dressings were applied.

When the epiphyseal line disappears an operation is to be performed for the correction of the coxa vara.

Fig. 28 (case 10).—Right congenital coxa vara.

SUMMARY AND CONCLUSIONS

A complete review is here presented of ten cases of congenital coxa vara. Eight of the patients were children, and two were adults. Four of them were males and six were females. Three of the children were colored. The two adults were white. In four of the cases the involvement was bilateral, and in six only one hip was involved. In four of the cases in which the lesion was unilateral the left hip was involved, in two, the right.

A complete review of the history of congenital coxa vara is presented.

The etiology of the condition is not known. The various theories are presented.

The microscopic appearance of the lesion shows nothing characteristic.

The history of the specific case is suggestive of congenital coxa vara, and the case must be differentiated from congenital dislocation, especially if the lesion is bilateral.

The roentgen appearance is unusual and thoroughly pathognomonic. If one is not familiar with the roentgen appearance, the coxa vara will probably be misinterpreted as a fracture of the neck of the femur with nonunion.

The prognosis is governed by the treatment employed.

The conservative treatment (heretofore the only treatment employed) is obsolete. The proper procedure consists of two surgical phases: (1) Bony union should be produced in the defective portion of the neck of the femur, preferably, in my opinion, by drilling, and (2) when this union is secure, the depressed neck of the femur should be elevated by a subtrochanteric wedge osteotomy.

NOTE.—Since this article was written I have seen a number of cases of congenital coxa vara, indicating that the condition occurs more frequently than I previously thought. I have also found it feasible to drill the neck of the femur to cause ossification in the defective portion of the neck and to do a subtrochanteric wedge osteotomy for the correction of the coxa vara at one operation.

Dr. Samuel Kleinberg permitted me to operate on several of these patients. Dr. Leo Mayer, Dr. Harry Finkelstein and Dr. Herman C. Frauenthal allowed me to use material from their services.

BIBLIOGRAPHY

Fiorani, G.: Concerning a Rare Form of Limping, Gazz. d. osp. **2**:717 (Aug. 30-Sept. 15) 1881.

Hofmeister, F.: Coxa Vara: A Typical Form of Curvature of the Femoral Neck, Beitr. z. klin. Chir. **12**:245, 1894.

Kredel, L.: Congenital Coxa Vara, Centralbl. f. Chir. **23**:969, 1896.

Kirmisson, E.: New Facts in the Study of the Rachitic Incurvation of the Femoral Neck (Congenital Coxa Vara), Rev. d'orthop. **8**:302, 1897.

Alsberg, A.: Anatomical and Clinical Considerations of Coxa Vara, Ztschr. f. orthop. Chir. **6**:106, 1898.

Alsberg, A.: Theory and Differential Diagnosis of Coxa Vara, Ztschr. f. orthop. Chir. **7**:365, 1899.

Whitman, R.: Further Observations on Coxa Vara with Particular Reference to Its Aetiology and Treatment, New York M. J. **69**:73, 1899.

Luss, A.: Anatomical Contributions to Coxa Vara, Inaug. Dissert., Würzburg, Becker's Universitäts Buchdruckerei, 1899, p. 1.

Mouchet, A., and Aubion, P.: Congenital Coxa Vara, Gaz. hebd. de méd. et de chir. **4**:481, 1899.

Bennett, W. E.: Coxa Vara, Birmingham M. Rev. **48**:321, 1900.

Reiner, M.: Relation of Congenital Coxa Vara to Congenital Defect of the Femur, Ztschr. f. orthop. Chir. **12**:297, 1903.

Hoffa, A.: Congenital Coxa Vara, Deutsche med. Wchnschr. **31**:1257 (Aug. 10) 1905.

Feiss, H. O.: Congenital Coxa Vara, J. A. M. A. **46**:565 (Feb. 24) 1906.

Francke: Case Reports on Congenital Coxa Vara, Ztschr. f. orthop. Chir. **15**:288 (July) 1906.

von Kryger, M.: The Etiology of Coxa Vara, Festschrift, Isidor Rosenthal, Leipzig, Georg Thieme, 1906, pt. 2, p. 257.

Helbing, C.: Coxa Vara: An Analysis of the Material from Hoffa's Private Clinic, Ztschr. f. orthop. Chir. **15**:502, 1906.

Ghuilamila, J. D.: Congenital Coxa Vara and Tuberculous Coxitis, Ztschr. f. orthop. Chir. **18**:181, 1907.

Frisch, O.: A Case of Coxa Vara Congenita, Wien. klin. Wchnschr. **21**:1558, 1908.

Rafilsohn, E.: Coxa Vara Congenita, Inaug. Dissert., Emmendingen, 1908, p. 1.

Spitzy, H.: How Often Is Congenital Coxa Vara Found in Association with a Luxation of the Hip Joint? Verhandl. d. deutsch. f. Gesellsch. d. orthop. Chir., 1909, p. 19.

Drehmann, G.: Contributions to the Etiology and Therapy of Coxa Vara, Verhandl. d. deutsch. Gesellsch. f. orthop. Chir., 1909, p. 360.

Hohmann, G.: Contribution to the Pathology and Therapy of Coxa Vara, München. med. Wchnschr. **57**:1219 (June 7) 1910.

Mayer, E.: Case of Severe Bilateral Congenital Coxa Vara, Ztschr. f. orthop. Chir. **25**:323, 1910.

Drehmann, Gustav: On the Question of Congenital Coxa Vara, Berl. klin. Wchnschr. **47**:1752, 1910.

Mouchet, A., and Segard, M.: Congenital Coxa Vara, Bull. Soc. anat. de Paris **87**:114 (March) 1912.

Mouchet, A., and Segard, M.: Congenital Coxa Vara, Paris méd. **1**:421 (March 30) 1912.

Delitala, F.: Coxa Vara Congenita, Arch. di ortop. **30**:382, 1913.

Schwarz, E.: About Coxa Vara Congenita, Beitr. z. klin. Chir. **87**:685, 1913.

Bley, K.: Coxa Vara, Inaug. Dissert., Dortmund, Lensing, 1913.

Elmslie, R. C.: Coxa Vara, Its Pathology and Treatment, London, Henry Frowde, 1913.

Perrier: Infantile Coxa Vara, Rev. d'orthop. **5**:157, 1914.

Brand, B.: Coxa vara congenita bilateralis, Nederl. tijdschr. v. geneesk. **60**:518 (Feb. 5) 1916.

Lepoutre: Congenital Coxa Vara, Bull. et mém. Soc. d. chirurgiens de Paris **47**:922, 1921.

Nilsonne, H.: Contribution to the Knowledge of Congenital Coxa Vara, Acta radiol. **3**:383 (Nov. 10) 1924.

Noble, T. P., and Hauser, E. D.: Coxa Vara, Arch. Surg. **12**:501 (Feb.) 1926.

Fairbank, H. A. T.: Unusual Case of Congenital Coxa Vara, Proc. Roy. Soc. Med. **20**:237 (Jan.) 1927.

Peabody, C. W.: Bilateral Defect of Femoral Heads, J. Bone & Joint Surg. **9**:288 (April) 1927.

Fairbank, H. A. T.: Infantile or Cervical Coxa Vara, in Robert Jones' Birthday Volume, New York, Oxford University Press, 1928, p. 225.

Nilsonne, H.: On Congenital Coxa Vara, Acta chir. Scandinav. **64**:217 (Nov. 22) 1928.

Barr, J. S.: Congenital Coxa Vara, Arch. Surg. **18**:1909 (April) 1929.

Jansen, M.: The Large Brim, the Wide Pelvic Girdle and the Outstanding Number of Hip Anomalies in Man, J. Bone & Joint Surg. **11**:461, 1929.

Kreuz, L.: A Critical Review of the Morphology of Congenital Coxa Vara, Arch. f. orthop. u. Unfall-Chir. **28**:106, 1930.

Bargellini, D.: Evolution of Congenital Coxa Vara, Arch. ital. di chir. **27**: 578 (Nov.) 1930.

Sacerdotte, Gabriele: A Case of "Alternate" Coexistence of Luxation of the Hip and Congenital Coxa Vara, Minerva med. **1**:614 (April 21) 1931.

IRRADIATION IN THE TREATMENT OF TUMORS OF THE PITUITARY GLAND

REPORT OF TWENTY-THREE CASES

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During the past decade increasing interest has been shown in the treatment of tumors of the pituitary gland by high voltage irradiation. Approximately twenty-six years ago, impetus was given to this form of treatment by Gramegna[1] (1909), who was the first to report treatment by this method of a tumor of the pituitary gland. His patient, an acromegalic woman with rapidly failing vision, was given two courses of treatment in the years 1907 and 1908, respectively. The first was followed by some improvement in her vision, which later failed. She was not helped by the second course of treatment. He felt that the acromegalic features of the case were arrested. The radiation was given through the mouth, as being the nearest portal of entry to the pituitary gland and offering relatively little bony resistance to the rays. He felt that the mucous membranes tolerated irradiation as well as, or better, than the skin, and that the brain and other normal tissues of the central nervous system, such as the optic nerves, were not injured by the treatment.

Greater attention has been paid to irradiation of chiasmal lesions in Europe than in this country. Magnus[2] (1928), Nordentoft[3] (1928), Béclère[4] (1922 and 1929), Sgalitzer[5] (1929), Fraticelli[6] (1930),

1. Gramegna, A.: Un cas d'acromégalie traité par la radiothérapie, Rev. neurol. **17**:15, 1909.

2. Magnus, Hans: Röntgenbestrahlungen der Hypophysentumoren, nebst Bemerkungen über hemianopische Pupillenstarre, Arch. f. Ophth. **121**:225 (Oct. 13) 1928.

3. Nordentoft, Jacob: Bons effets de la radiothérapie dans un cas de tumeur hypophysaire, J. radiol. et d'électrol. **12**:280 (June) 1928.

4. Béclère, M. A.: Technique, resultats, indications et contre indications de la roentgenthérapie des tumeurs hypophysaires, Rev. neurol. **38**:808, 1922; Les adénomes hypophysaires de l'adolescence et de l'enfance justiciables de la radiothérapie, ibid. **1**:463, 1929.

5. Sgalitzer, Max.: Erfahrungen mit der Röntgenbehandlung bei Hypophysengeschwülsten, Wien. med. Wchnschr. **79**:566, 1929.

6. Fraticelli, Aureliano: La roentgenterapia nei tumori ipofisari a sindrome chiasmatica: tecnica e risultati, Atti di ottal. e ocul. **58**:756, 1930.

Jusefowa, Czerny and Heinismann [7] (1930) and Nemenow and Jugenburg [8] (1928) have reported series of cases in which this treatment was given. The consensus seems to be that temporary improvement of visual disorders resulting from the pressure of a tumor of the pituitary gland on the optic chiasm follows high voltage treatment. One of Nemenow's patients retained practically normal vision for seven years following treatment. Béclère expressed the belief that irradiation does not completely stop the evolution of the adenoma, but felt that it should be tried before resorting to surgical intervention. Jusefowa, Czerny and Heinismann advised decompression prior to irradiation in cases showing increased intracranial pressure. Most observers are in agreement that acromegalic symptoms in general have been arrested by high voltage treatment.

In this country less attention has been paid to irradiation of tumors of the pituitary gland, more emphasis having been placed on their surgical treatment. Frazier and Grant [9] (1925), in reviewing one hundred cases of pituitary lesions, stated that there were only three in which unquestionably the lesions were favorably affected by irradiation, and they doubted the permanency of these results. They did not state how many patients of the series received high voltage irradiation. Later, in 1930, Frazier,[10] in a report of a larger series of pituitary disorders, two hundred and thirty-one cases, again discussed the question of irradiation. Ten cases were reported in detail, in two of which the patients received high voltage irradiation. One received three courses, with marked improvement for more than three years. He stated: "This is the only case in my experience in which the beneficial effects of irradiation have been sustained." The second patient was not helped by one series, and was subsequently improved by transfrontal craniotomy. Frazier asked: "Under what circumstances is one warranted in trying the effects of irradiation, with the risk of what delay in operation may mean?" He based his answer, not so much on the distortions of the field as on the appearance of the disk. He felt that if the capillarity of the disk is essentially normal operation can be postponed with propriety, but that, as is frequently the case when the

7. Jusefowa, F. L.; Czerny, L. I., and Heinismann, I.: Roentgen Therapy in Tumors of the Area of the Hypophysis, Klin. Monatsbl. f. Augenh. **85**:344 (Sept.) 1930.

8. Nemenow, M., and Jugenburg, Anna: Die Strahlenbehandlung der Hypophysentumoren, Strahlentherapie **30**:238, 1928.

9. Frazier, C. H., and Grant, F. C.: Pituitary Disorder: A Digest of One Hundred Cases with Remarks on the Surgical Treatment, J. A. M. A. **85**:1103 (Oct. 10) 1925.

10. Frazier, C. H.: A Series of Pituitary Pictures; Commentaries on the Pathologic, Clinical and Therapeutic Aspects, Arch. Neurol. & Psychiat. **23**:656 (April) 1930.

patient is already blind in one eye and vision is rapidly failing in the other, procrastination is never justifiable. He emphasized the fact that irradiation will have no influence on a pituitary lesion which is already cystic, and added that there is no way, except by operation, of determining the precise nature of the lesion. Towne [11] (1926 and 1930) reported a series of five cases of tumor of the pituitary gland treated by roentgenotherapy. Two cases reported in 1926 were again reviewed in his 1930 report. In general, he summarized the situation as follows: "Eighty per cent of pituitary adenomas are solid, and twenty per cent are cystic. Twenty per cent of patients retain useful vision for more than five years after operation; eighty per cent show no improvement or, after more or less marked improvement, have recurrences after about two years. Operative treatment of pituitary adenomas has a mortality ranging from 7 per cent upward; roentgen-ray treatment has no mortality." Cases were reported showing long-standing favorable results from roentgen treatment and likewise showing that if irradiation does not give good results, a diagnosis of cystic tumor, favorable for operation, may be made. He felt that all pituitary adenomas should be treated by roentgen rays under the observation of an ophthalmologist and a neurosurgeon, and that surgical intervention should be undertaken short of six months only when visual acuity and the fields recede under roentgen treatment. Dyke and Gross,[12] in 1931, discussed roentgenotherapy of tumors of the pituitary gland, and reported five cases in which it was given. They stated that for some years it has been Elsberg's opinion that every patient with defects of the visual fields due to a pituitary neoplasm should first receive a course of high voltage therapy. This should be continued if improvement occurs. If, on the other hand, the visual fields and acuity recede, surgical intervention is indicated. Like Towne, they looked on irradiation as a diagnostic test to separate the patients requiring surgical intervention from those not immediately requiring it. Three of their patients, presumably having adenomas, showed definite improvement in both visual fields and visual acuity. The headache was entirely relieved. The two remaining patients showed no further loss of vision, although they were said to have improved subjectively. Dyke and Gross mentioned an additional case, in which the patient had been treated elsewhere with only temporary improvement. At operation later the lesion proved to be a cystic adenoma. One patient of their series, with acromegaly and

11. Towne, E. B.: Roentgen-Ray Treatment of Pituitary Tumors, Arch. Neurol. & Psychiat. **15**:92 (Jan.) 1926; Treatment of Pituitary Tumors: The Rôle of the Roentgen Ray and of Surgery Therein, Ann. Surg. **91**:29 (Jan.) 1930.

12. Dyke, Cornelius G., and Gross, Sidney W.: The Roentgenotherapy of Pituitary Tumors, Bull. Neurol. Inst. New York **1**:211 (June) 1931.

presumably a chromophil adenoma, was improved. Heuer,[13] in 1931, gave an excellent résumé of the surgical treatment of tumors and other lesions about the optic chiasm. His closing words concerning irradiation of the lesions summarize his attitude. He stated:

> The X-ray has been a distinct contribution to the treatment of hypophyseal adenomata, both chromophil and chromophobe. In certain cases it may check the growth of the tumor and delay or make unnecessary its operative partial removal. It is a valuable adjunct and should in our opinion be used routinely in the post-operative treatment of these tumors. It is possible that the improvement in the results of the operative treatment of hypophyseal adenomata, attributed in part by us to the more logical removal of that portion of the tumor directly compressing the chiasm and nerves, may in greater part be due to more frequent use of post-operative X-ray treatments. The use of this method is not without danger. Its use as an alternative to surgery presupposes accurate pathological diagnosis, for, so far as our present knowledge goes, the hypophyseal adenomata alone of the many lesions about the chiasm respond to it. Its indiscriminate use in lesions about the chiasm may do great harm; and it should in our opinion be given only with the knowledge and consent of those familiar with these lesions.

Sachs[14] (1931), in discussing the treatment of tumors of the pituitary gland, favored surgical intervention, although in discussing two cases of chromophil adenoma in which operation was done with beneficial results, he expressed the opinion that both cases could have been equally well arrested with high voltage therapy. He added: "Certainly, in the light of our present knowledge, one should try this first, before resorting to operation." Cushing[15] (1932) was anything but enthusiastic regarding irradiation of the lesions. He stated:

> So far as concerns radiotherapeusis, at least in the case of the chromophobe adenomas, it is safe to say that it will come to be discarded just as radiation for exophthalmic goitre has been, so soon as neurosurgeons as a class perfect themselves in the details of the operative procedure. It may reasonably be assumed that in those clinics where radiation for these lesions is still routinely advocated, the surgical results have been poor and the mortality disturbingly high.

He added in a footnote: "The chromophile adenomas in our experience appear to be more definitely susceptible to radiation."

Homans[16] (1932) was somewhat more enthusiastic regarding irradiation of both chromophobe and chromophil adenomas. He stated: "In both forms of adenoma, radio-therapy is beneficial and may deserve

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13. Heuer, George J.: The Surgical Approach and the Treatment of Tumors and Other Lesions About the Optic Chiasm, Surg., Gynec. & Obst. **53**:489 (Oct.) 1931.

14. Sachs, Ernest: Diagnosis and Treatment of Brain Tumors, St. Louis, C. V. Mosby Company, 1931, p. 296.

15. Cushing, Harvey: Intracranial Tumours, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 79.

16. Homans, John: A Textbook of Surgery, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 564.

a trial before recourse is had to surgery. The chromophile adenomas appear to be particularly susceptible to the effects of radiation." Bailey [17] (1933) stressed the point that effective treatment of pituitary adenomas can be controlled only by carefully examining the visual fields. He was not adverse to, and even recommended, high voltage therapy in such cases, provided the vision is not jeopardized. He stated:

> The growth of an adenoma can sometimes be retarded and even a regression in size obtained by persistent roentgen-radiation. This observation has been often repeated and certainly, if there is no immediate danger to vision, roentgen-radiation should be tried in every case. It should not be forgotten, however, that serious accidents may occur, noticeably from edema or from hemorrhage into the tumor immediately after too energetic radiation. In either case vision rapidly fails and prompt operation is necessary.

Globus [18] (1933) considered that surgical intervention in adenoma of the pituitary gland yielded the most satisfactory results. Regarding high voltage therapy, he stated:

> Occasionally high voltage roentgen or radium therapy may give rise to apparent improvement and to the false hope that the pathologic process has been arrested. However, in the course of time an explosive reappearance of symptoms will shatter one's belief that the disease process may remain permanently dormant. Unfortunately, at such a time the expanded lesion has extended into such regions as to make a surgical approach prohibitive.

He cited the case of a woman, aged 31, who had unmistakable signs of tumor of the pituitary gland which showed its presence by amenorrhea for sixteen years. At the age of 26 the diagnosis of tumor of the pituitary gland was made. A bitemporal hemianopia existed at that time. After an unsuccessful attempt to remove the growth by an intranasal approach, radiotherapy was instituted, with gratifying improvement and widening of the visual fields. This improvement was maintained for five years. Following this the patient showed signs of intracranial extension of the growth, and apparently died during a craniotomy for removal of the growth. He commented that removal of the tumor at an earlier stage might have altered the sequence of events. The autopsy showed a relatively small tumor of the pituitary gland, with a large extension in the interpeduncular space and invasion of the third ventricle. He did not state the type of tumor. One wonders whether, after having five years of relief from radiotherapy, her life might not have been prolonged and improvement might have occurred again if further radiotherapy, instead of surgery, had been adopted.

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17. Bailey, Percival: Intracranial Tumors, Springfield, Ill., Charles C. Thomas, Publisher, 1933, p. 111.

18. Globus, J. H.: Tumors Affecting the Optic Chiasm and Optic Tracts: A Brief Critical Survey of Their Clinical and Anatomic Features, Arch. Ophth. **9**:729 (May) 1933.

The use of high voltage therapy was concretely brought to the attention of one of us (C. W. R.) in 1920, when a patient having a symptomatic chromophobe adenoma was given irradiation by Dr. Albert Soiland of Los Angeles. The patient, a man, had a temporal hemianopia on the right, and a loss of vision in the lower fields on the left, general hypopituitary symptoms, and a greatly enlarged sella turcica with atrophy of the posterior clinoidal processes. Primary optic atrophy was present on both sides. The treatments were given through four portals of entry, cross-firing the hypophysis. The exact dosage cannot be computed in the terms of units now employed, but he is said to have received doses from a high potential source. His vision soon began to improve, and his headaches disappeared. Subsequently, high voltage treatments were given him in Stockholm. Ten years later he was reported as being free from headaches, having serviceable vision and being clinically well. The case is not included in this series, as the details were not sufficiently followed to permit its use as an accurate clinical record. However, there is little doubt that the patient was greatly benefited by high voltage radiation, and that the period of improvement has lasted for more than a decade.

REPORT OF CASES

CASE 1.—*Advanced pituitary tumor with acromegaly, probable chromophil adenoma (unverified). Blind in the right eye; temporal hemianopia in left visual field; headaches. Marked improvement in left visual field nine years after one course of high voltage irradiation.*

E. G., a woman, aged 54, married, a housewife, was referred by Dr. A. P. Maisch, Los Angeles, on June 11, 1924. Failing vision had been noticed since 1919. During 1919 there was a period of terrific headaches associated with nausea and vomiting and accompanied by two convulsions. Later the headaches became less severe; marked mental changes in the nature of *Witzelsucht* and considerable weakness of the left leg developed.

Examination revealed an acromegalic woman about 5 feet, 3 inches (160 cm.) tall, weighing 145 pounds (65.8 Kg.). The hands were thick and spadelike, the feet large and the features coarsened, with an increased growth of hair on the face. She was completely blind in the right eye, and ocular movements on this side were limited. The right pupil was dilated and did not react to direct light, but reacted consensually. The left pupil was smaller and reacted to direct light, but not to consensual light. There was advanced primary optic atrophy on both sides, the disks being sharply outlined and very pale. The veins were large, but the arteries were almost threadlike. The deep reflexes were increased on the left side. No abnormal reflexes of the Babinski group were present. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed marked enlargement of the sella turcica and rarefaction and thinning of the floor of the posterior clinoid processes (fig. 1).

Operation was advised, but refused. Because of the refusal and the fact that the patient was fast becoming blind, a course of high voltage therapy was given. This was followed by a violent reaction, accompanied by headaches and hyperthermia. She remained in a semicoma for twenty-four hours, and exhibited signs

of increased intracranial pressure for two days subsequently. Figure 1 shows the visual fields on June 27, shortly before irradiation. It also shows the visual fields on Oct. 30, 1931, more than seven years later. On the left side, there is some improvement both in the fields and in acuity. We have recently been informed (June 4, 1933) that she is free from headaches and is mentally clearer, but has an occasional convulsion. On the whole, nine years after high voltage therapy, her general condition is better, and she has serviceable vision in her left eye.

Comment.—This patient was the first treated. She received only a moderate total dose of irradiation, but a larger initial dose than we were

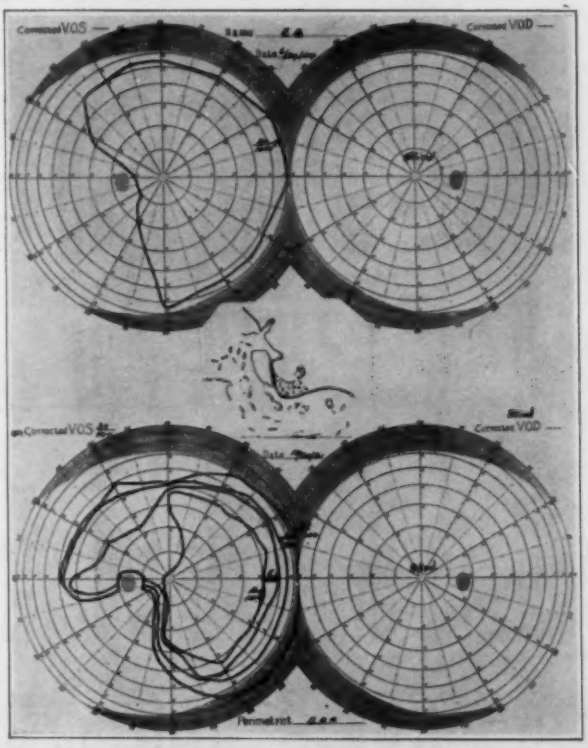

Fig. 1 (case 1).—Chromophil adenoma (unverified). The perimetric fields before irradiation are shown above, and those following irradiation below. While there was no return of vision in the blind right eye, vision was improved in the left for more than seven years. Operation was refused. The insert shows a tracing of the enlarged sella turcica. The posterior clinoid processes are practically obliterated.

in the habit of giving subsequently. She received approximately 300 roentgens (r) in two successive days, and a week later approximately 400 r at one treatment. She had the most violent reaction, following the last treatment, of any patient of the series, consisting of nausea, vomiting and convulsions; in fact, she had the only reaction that was alarming. Prior to treatment she showed signs of increased intracranial

Summary of Cases

Case	Sex	Age	Duration of Visual Disturbances and Hypophyseal Symptoms	Type of Tumor	High Voltage Therapy	Operative Procedure	Comment
1	F	54	5 yrs.; in right eye, complete blindness; in left, atypical temporal hemianopia; headaches; acromegaly	Chromophil adenoma (unverified)	3 single doses in 10 days	Operation refused	No improvement in right eye (blind); improvement in left eye lasting 9 yrs.; no advance in acromegaly; headaches relieved
2	M	23	3 yrs.; in right eye, temporal hemianopia; left eye blind; hypopituitarism	Chromophobe adenoma (grossly verified)	2 series—second one short	Exploration of pituitary region; partial removal of mulberry-like tumor, followed by high voltage therapy	No improvement of vision following preoperative irradiation; improvement in right eye for 1 yr. following operation; ultimate blindness; death 2 yrs. later; autopsy refused
3	M	42	Failing vision in right eye 2 mos.; in left, 10 yrs.; bitemporal hemianopia; headaches; hypopituitarism	Chromophobe adenoma (unverified)	3 series—second short	None	Definite improvement of visual fields and acuity for more than 6 yrs.; headaches relieved
4	F	50	Failing vision in right eye 3 yrs., going on to practical blindness; in left eye vision remaining only in upper nasal quadrant	Adenocarcinoma (verified)	1 series, irregular	Exploration of pituitary region; partial removal of adenocarcinoma	No improvement of vision following irradiation; death following operation; autopsy refused
5	M	49	3½ yrs.; atypical bitemporal hemianopia	Adenocarcinoma (verified)	5 series, followed by radium therapy	Exploration; adenocarcinoma of the pituitary gland found; partial removal	Slight improvement of fields following early irradiation which soon ceased; vision worse 15 mos. later
6	M	16	1 yr. bitemporal hemianopia; headaches; hypopituitarism	Chromophobe adenoma (unverified)	2 series—second short	None	Improvement in vision for more than 3 yrs.; headaches relieved; grew to 6 feet and gained 16 pounds
7	F	32	9 mos. bitemporal hemianopia, marked, contraction of fields; amenorrhea, 2 yrs.	Chromophobe adenoma (unverified)	2 series	None	Improvement of visual fields for more than 3 yrs.; amenorrhea persisted
8	F	48	5 mos.; island of vision in right lower nasal quadrant; left temporal hemianopia; headaches	Chromophobe adenoma (verified)	2 series preoperatively	Exploration of pituitary region; partial removal of chromophobe adenoma	Vision in right eye stationary after 2 yrs.; vision in left eye improved after 2 yrs.; headaches relieved
9	M	39	2 yrs.; right eye, failing vision; bitemporal hemianopia when seen	Cystic chromophobe adenoma (unverified)	1 series	Operation refused	Continued failure of vision; should have exploration
10	M	40	4 yrs.; atypical bitemporal hemianopia; diabetes insipidus (?); headaches; hypopituitarism	Chromophobe adenoma (unverified)	Yes*	Operation refused	Temporary improvement; should have exploration
11	F	41	3½ yrs.; failing vision; right eye almost blind; left eye, temporal hemianopia	Chromophobe adenoma (unverified)	Yes*	Operation refused	Slight improvement in left eye for more than 4 yrs.; little improvement in right eye

12	F	44	7 mos.; failing vision; bitemporal hemianopia; greatest visual disturbance in left eye; headaches	Cystic chromophobe adenoma (verified)	Yes*	Exploration of pituitary region; partial removal of cystic chromophobe adenoma	Temporary improvement of vision following irradiation and surgery, now failing; duration of improvement, 2 yrs.; marked gain in weight following operation
13	F	36	Visual disturbance slight; acromegaly advanced; severe headaches, 6 yrs.	Chromophil adenoma (unverified)	2 series, 2 years apart	Right subtemporal decompression	Return of visual fields to normal; no improvement in headaches; acromegalic features unchanged
14	M	68	18 mos.; bitemporal hemianopia; greatest disturbance on right	Chromophobe adenoma (verified)	1 series	None	Vision gradually improved for more than a year; death of apoplexy; chromophobe adenoma disclosed at autopsy; histologic study reveals no tissue change attributable to irradiation
15	M	47	10 yrs.; failing vision; advanced bitemporal hemianopia; mild hypopituitarism	Chromophobe adenoma (unverified)	2 series	None	Definite improvement in fields maintained for more than 3 yrs.
16	M	42	5 yrs.; advanced bitemporal hemianopia; severe headaches	Chromophobe adenoma (unverified)	2 series*	Operation refused	Definite improvement in fields maintained for more than 2 yrs.; complete relief from headaches
17	M	39	1 yr.; failing vision; atypical bitemporal hemianopia; hypopituitarism	Chromophobe adenoma (unverified)	2 short series	Operation refused	Moderate improvement of fields continued for 18 mos.
18	M	44	4 yrs.; right eye, small island of vision in upper nasal quadrant; left eye, practically complete blindness; severe headache; Wassermann ++++; acromegaly	Chromophil adenoma (unverified)	3 series postoperatively	Attempted exploration of pituitary region: first stage and decompression	Parent's vision in both eyes returned practically to normal and maintained 2 yrs.; headaches relieved
19	M	49	5 yrs.; failing vision; atypical hemianopia, most marked in left eye; headaches	Chromophobe adenoma (unverified)	1 series	Operation refused	Further failure of vision in left eye; definite improvement of vision in right eye maintained more than a year; should have exploration
20	M	32	6 yrs.; failing vision in right eye; later, almost blind; temporal hemianopia in left eye	Chromophobe adenoma (grossly verified)	1 series	Operation refused	No improvement during observation; sudden death following an explosion; coroner reported, "gliomatous tumor occupying sella turcica;" undoubtedly adenoma; specimen unavailable for study
21	F	30	2 mos.; atypical bitemporal hemianopia; headaches; hypopituitarism; amenorrhea 9 yrs.	Cystic chromophobe adenoma (verified)	1 series	Exploration of pituitary region; emptying of cyst and partial removal of adenoma	No improvement of fields following irradiation; return of fields to normal within 2 wks. after operation
22	F	27	1 yr.; atypical bitemporal hemianopia; headaches; mild acromegaly	Chromophil adenoma (unverified)	1 series	None	Marked improvement of fields 5 mos. after irradiation
23	F	40	3 wks.; atypical hemianopia; acromegaly 3 yrs.; diabetes 6 wks.; headaches; abducens palsy on right	Chromophil adenoma (unverified)	1 series	None	Return of fields to normal 3 mos. after irradiation; disappearance of abducens palsy on right; headaches markedly decreased

* Treated elsewhere, details not known.

pressure, and possibly the intense reaction was due to further increase of pressure from postirradiation congestion in the tumor. This made us cautious in the amount of radiation administered in subsequent cases. In most, if there was a temporary increase in the headaches or increased blurring of vision, we either decreased the dose or lengthened the intervals between treatments.

CASE 2.—*Pituitary tumor; probable chromophobe adenoma (grossly verified). Hypopituitarism. Incomplete operative removal, followed by high voltage irradiation. Total blindness in left eye, uninfluenced. Vision in right eye temporarily improved, but later lost.*

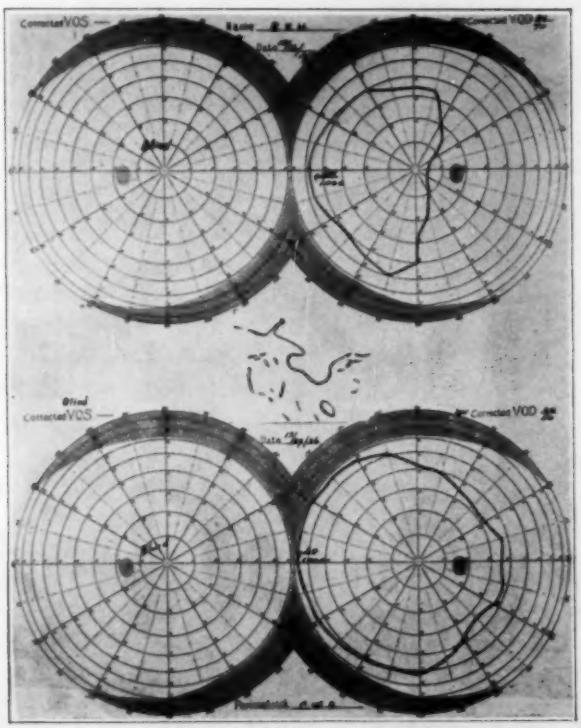

Fig. 2 (case 2).—Chromophobe adenoma (grossly verified). Above are the perimetric fields before irradiation or operation, and below are the fields one year subsequent to partial removal of the tumor followed by a course of high voltage therapy. The insert shows a much enlarged sella turcica invading the sphenoid sinuses, and the absence of posterior clinoid processes.

B. F. H., a man, aged 23, single, a tutor, was referred by Dr. F. B. Clarke, Long Beach, Calif., on Dec. 14, 1925. There had been failing vision in the left eye for three years and in the right eye for the preceding few months. At the time of our first examination, the patient was totally blind on the left side, with a temporal hemianopia on the right (fig. 2). There had been a period of severe headaches

three years previously. At the time of examination, headaches were infrequent and mild.

Examination revealed a man, 5 feet, 7 inches (170.1 cm.) tall, weighing 190 pounds (86.2 Kg.), obese, of feminine build and showing characteristics of hypopituitary disturbance. The right disk was choked, and the left showed hazy margins, the disk itself being distinctly pale. The latter appeared to be a secondary atrophy following an old choked disk. There was palsy of the external rectus muscle on the left. The right pupil did not react to direct light; the left reacted sluggishly. The Wassermann reaction of the blood was negative. Roentgenograms of the skull on December 16 showed erosion of the posterior clinoid processes; the floor of the sella turcica was practically gone, and there was marked enlargement of the region of the sella turcica (fig. 2).

On Dec. 6, 1925, and Jan. 2, 1926, a two stage operation was performed, and a left frontal approach of the pituitary gland was carried out. An oval, mulberry-like tumor was found, which was highly vascular, and was only partially removed. Four and a half months following the operation he was given fairly vigorous high voltage therapy, with some improvement in vision on the right for approximately twelve months (fig. 2). He died on March 19, 1927, and at that time had only perception of light in the right eye. Permission for autopsy was not obtained.

Comment.—The tumor in this case was partially removed at operation, and decompression was carried out five and a half months prior to high voltage therapy. The treatment was given fairly rapidly without untoward reaction. In spite of both methods of treatment and temporary improvement, the patient's vision completely failed, and death occurred approximately two years after the patient came under observation.

CASE 3.—*Pituitary tumor; probable chromophobe adenoma (unverified). Bitemporal hemianopia; headaches; hypopituitarism. Improvement maintained for more than six years following high voltage irradiation.*

H. J. F., a man, aged 42, married, a rancher, was referred by Dr. George W. McCoy, Los Angeles, on Sept. 7, 1926. There had been failing vision in the left eye for the previous ten years. About two months before coming under our observation vision in the right eye began to fail. At our first examination the visual fields showed a fairly typical bitemporal hemianopia (fig. 3). During this time he had been having rather severe frontal and bitemporal headaches. These headaches were intermittent, usually lasting from one to two days at a time. He tired easily.

Examination revealed a man 5 feet, 7 inches tall, weighing 150 pounds (68 Kg.). His skin was rather dry and the beard was not as heavy as formerly, both moderate characteristics of hypopituitary disturbance. The eyegrounds showed both disks sharply outlined, with clear optic cups and moderate temporal pallor. The left disk was paler than the right. The Wassermann reaction of the blood was negative. The neurologic examination revealed no abnormality. Roentgenograms of the skull showed a complete loss of the posterior clinoid processes, with considerable absorption of the anterior processes. The sella turcica was enlarged and the floor depressed (fig. 3).

Comment.—The patient was given high voltage treatment, with definite improvement of the visual fields which has lasted over six years (fig. 3). He received three moderate courses of high voltage irradiation

without much reaction. The first was unsatisfactory from a roentgenologic point of view, because of small doses, 150 r three times a week for three weeks; the other two, because of irregularity in the time of treatments. However, clinically the patient was benefited for more than six years.

CASE 4.—*Adenocarcinoma of the pituitary gland (verified). No improvement following high voltage therapy. Death following operation.*

G. F. R., a woman, aged 50, married, a housewife, was referred by Dr. C. B. Walker, Los Angeles, on Oct. 19, 1928. For about eight years she had been

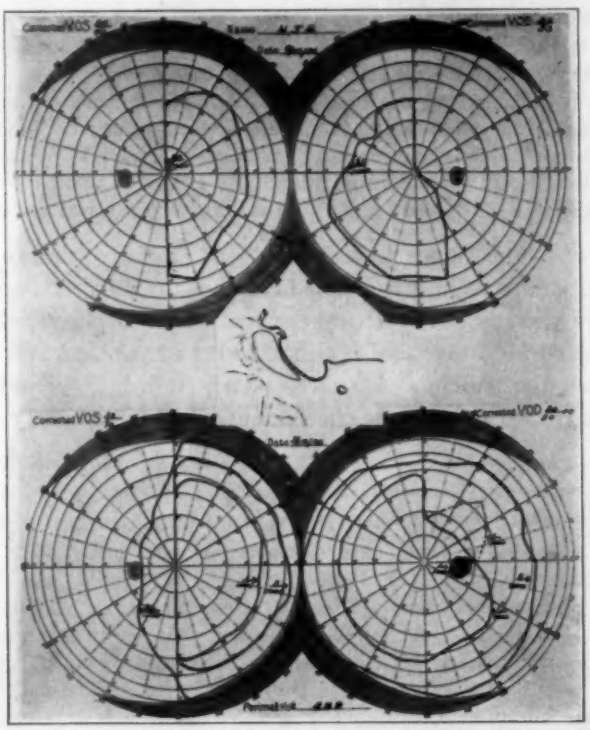

Fig. 3 (case 3).—Chromophobe adenoma (unverified). In the upper fields the fairly typical bitemporal hemianopia which existed before high voltage therapy (1926) is seen, while the fields below show the marked improvement following one course of high voltage irradiation. The improvement lasted for more than six years. The insert shows a tracing of the sellar region. The sella turcica is of the large, flattened type, with the posterior clinoid processes practically absent and little invasion of the sphenoid sinuses.

subject to sick headaches, which, during the preceding three years, had decreased. Since then she had failing vision, which went on to almost complete blindness in the right eye and low vision in the left (fig. 4).

Examination revealed an undersized, undernourished woman, with few, if any, general characteristics of pituitary disorder. There was double primary optic atrophy, with marked contraction of the vessels. The left pupil was larger than the

right, and both were practically static to light. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed enlargement of the sella turcica, with marked thinning of the floor and complete absorption of the posterior clinoid processes (fig. 4).

She was given a course of high voltage therapy consisting of twelve doses of 200 r given at irregular intervals during a period of four weeks. In spite of this her vision continued to fail, and irradiation was stopped on November 25. By Feb. 7, 1929, she was completely blind in the right eye (fig. 4). She was operated on in February, at which time a mulberry-like hypophyseal tumor was found. Small portions were nibbled away. Microscopic examination revealed evidence of

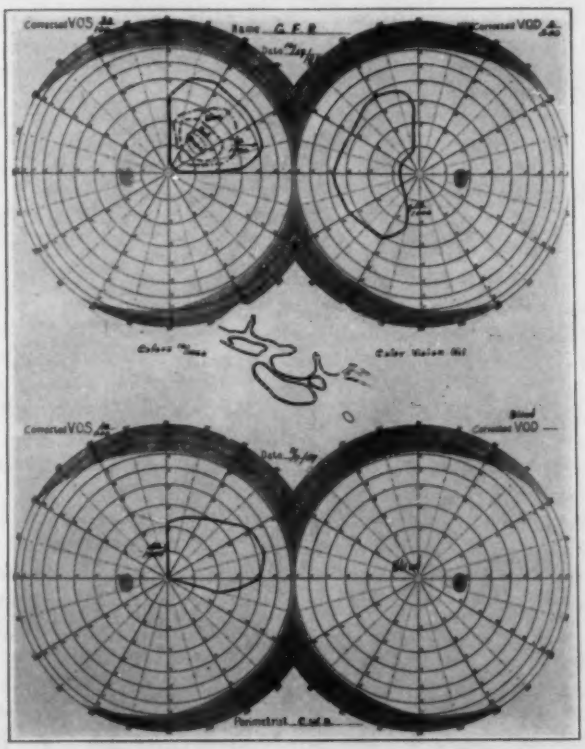

Fig. 4 (case 4).—Adenocarcinoma (verified). Above are the perimetric fields before irradiation, showing temporal hemianopia on the right and the remaining field of vision in the upper nasal quadrant on the left. Below, the fields show the loss of vision following roentgen irradiation four months later. The insert shows a moderately enlarged sella turcica with little destruction of the anterior or posterior clinoid processes and little encroachment on the sphenoid sinuses.

adenocarcinoma of the pituitary gland. Following the operation cerebral edema developed, and the patient died twelve hours later.

Comment.—This patient had treatment over a period of five weeks, which, from a roentgenologic point of view, was unsatisfactory because the treatments were given at irregular intervals. No favorable reaction followed the irradiation. Autopsy was not permitted.

CASE 5.—*Pituitary tumor, adenocarcinoma (verified). Temporary improvement following high voltage therapy and operation.*

H. G. E., a man, aged 49, married, a banker, was referred by Dr. H. Douglas Eaton, Los Angeles, on Sept. 13, 1929. The patient first noticed failing vision three and a half years previously, and for about three years had had considerable headache, especially on waking in the morning. During the previous year there had been little if any headache. The visual fields, when first seen, showed an atypical bitemporal hemianopia (fig. 5).

Examination revealed a man 5 feet, 7 inches tall, weighing 126 pounds (57.2 Kg.). He had a pasty look and was of the hypopituitary type, with dry

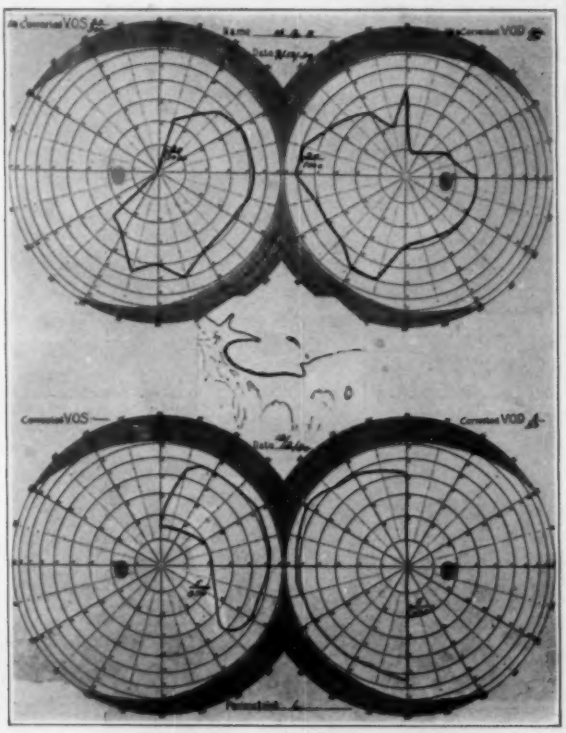

Fig. 5 (case 5).—Adenocarcinoma (verified). About are the visual fields before irradiation or surgical intervention, and below, the fields fifteen months later following an exploratory operation. The insert shows the enormously enlarged sella turcica, the posterior clinoid processes practically obliterated and the sphenoid sinuses entirely gone.

skin and scanty distribution of hair over the body. There was a primary optic atrophy on both sides, more advanced on the left than on the right side. The neurologic examination revealed no abnormalities. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed complete destruction of the sella turcica, with erosion of the floor. The posterior clinoid processes were practically gone. Apparently the growth had gone through the floor of the sella turica into the sphenoid sinuses (fig. 5).

He was given a course of high voltage roentgen therapy consisting of doses of 150 or 200 r four times a week for three weeks during October and November 1929, and in January 1930 a shorter similar course for two weeks. He showed considerable improvement in the visual fields (fig. 5). This improvement, however, soon began to fail, and he went to the Mayo Clinic on April 24, 1930, where he was operated on by Dr. Learmonth on May 2. An adenocarcinoma of the pituitary gland was found. A decompression area was provided. Following operation the patient was given three courses of high voltage treatment, the first from May 16 to May 20, the second from July 8 to July 11 and the third from September 8 to September 11. He was also treated by radium between October 7 and October 21. He returned to the Mayo Clinic in December 1930, at which time his vision was continuing to fail (fig. 5).[19]

CASE 6.—*Pituitary tumor; probable chromophobe adenoma (unverified) in an adolescent boy. Bitemporal hemianopia; headaches; hypopituitarism. Definite improvement in fields and headache following high voltage therapy.*

J. O. Jr., a boy, aged 16, a student, was referred by Dr. George W. McCoy, Los Angeles, on Nov. 1, 1929. For a year previously his vision had not been good. A bitemporal hemianopia was found on the first examination (fig. 6). Two months prior to examination he had troublesome headaches, which kept him from school. The headache was principally occipital.

Examination revealed a boy, 4 feet, 11 inches (149.8 cm.) tall, weighing 95 pounds (43 Kg.). He was undersized and distinctly of the feminine type. Secondary sexual characteristics had not developed. There was no evidence of hair on the body, and a beard had not started to grow. His voice was high-pitched. The skin was smooth, soft and dry. The eyegrounds showed a double primary optic atrophy with sharply outlined disks and marked pallor. The blood vessels were in good condition. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed marked enlargement of the sella turcica, with thinning of the posterior clinoid processes (fig. 6).

He was given two courses of high voltage therapy, following which there was marked improvement in the visual fields. The fields recorded on Aug. 28, 1931, showed approximately the maximum amount of improvement (fig. 6). The headaches disappeared. He returned to school, and the improvement of vision was still maintained after three years. In October, 1931, he was 5 feet, 5 inches (165.1 cm.) tall, weighed 111 pounds (50.3 Kg.) and was beginning to show signs of secondary sexual development.

Doses of 150 r four times a week were given continuously over a period of seven weeks in the first course, without any serious reaction or occasion to reduce the treatments. The second course, four months later, was short, and unfinished, and probably had little influence on the result.

CASE 7.—*Pituitary tumor; probable chromophobe adenoma (unverified). Bitemporal hemianopia; amenorrhea. Improvement of visual fields and acuity following irradiation. Amenorrhea uninfluenced.*

M. J., a woman, aged 32, unmarried, a stenographer, was referred by Dr. E. Richmond Ware, Los Angeles, on March 13, 1930. She first noticed failing

19. Dr. A. W. Adson of the Mayo Clinic provided the details regarding this patient's course while under observation at the clinic.

vision in the left eye in July 1929. This took the form of a temporal hemianopia. She did not recall when visual difficulties began in the right eye, but early in 1930 she became conscious of the fact that she could not see normally on that side. The visual fields taken at first examination showed a temporal hemianopia on the right and loss of vision, save for the upper nasal quadrant, on the left (fig. 7).

Examination revealed a woman about 5 feet, 7 inches tall, weighing 150 pounds. The neurologic examination revealed nothing important. The eyegrounds showed a primary optic atrophy on each side, but with fairly large arteries and veins persisting. Amenorrhea started at the age of 30. The Wassermann reaction of the

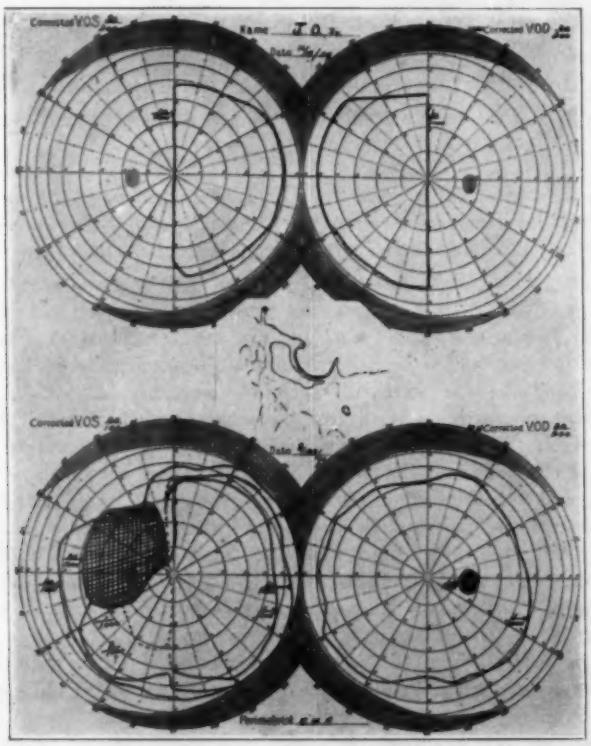

Fig. 6 (case 6).—Chromophobe adenoma (unverified). Above are the visual fields showing typical bitemporal hemianopia before irradiation, and below, the marked improvement following two courses of high voltage therapy. The insert shows moderate enlargement of the sella turcica with thinning of the posterior clinoid processes and beginning invasion of the sphenoid sinuses.

blood was negative. Roentgenograms of the skull showed moderate enlargement of the sella turcica and attenuation of the posterior clinoid processes (fig. 7).

A course of high voltage therapy was started on March 18. Within a few days the patient had headaches and showed marked contraction of visual fields, so that by April 3 the right field amounted to a small area of vision on the nasal side, and vision in the left eye was confined to a small area in the upper nasal quadrant. In spite of this, irradiation was continued, and the first course com-

pleted on April 28. Following a similar course of treatment in July and August there was marked improvement in the fields, which remained stationary for more than three years (fig. 7). Visual acuity improved on the right from 20/100 to 20/30.

Comment.—Although this patient's visual fields showed contraction during the early course of the high voltage therapy the treatment was continued in 150 r doses three times a week for six weeks. Treatment was then stopped for two months, after which a second, almost identical, course covering another period of six weeks was given. During the

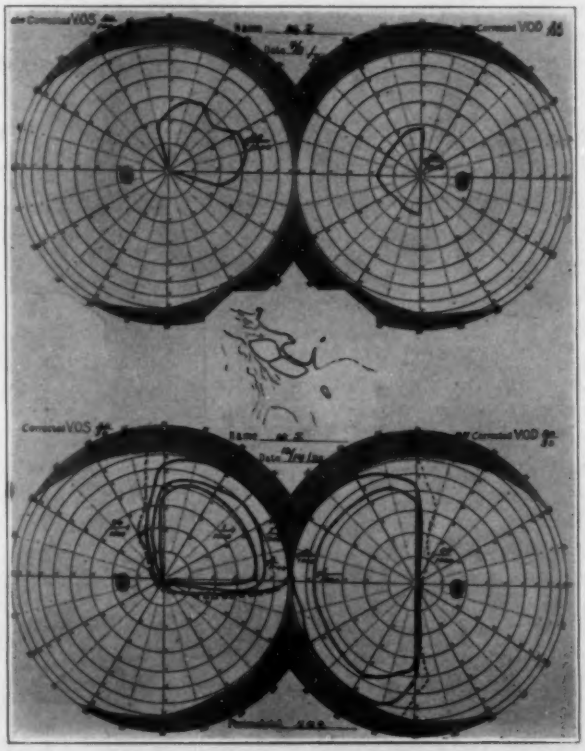

Fig. 7 (case 7).—Chromophobe adenoma (unverified). Above, the fields show the condition two weeks after the first course of irradiation was started. Constriction was temporarily increased as a result of irradiation. Below, the fields show the condition two years later following the second course of irradiation. The gain of vision has been maintained for more than three years. The insert shows the sella turcica moderately enlarged, with beginning erosion of the posterior clinoid processes.

second series of treatments the patient had no untoward reactions. The headaches disappeared. Should diminution of the fields occur again, further irradiation, if necessary followed by partial extirpation of the gland, will be carried out.

CASE 8.—*Pituitary tumor; chromophobe adenoma (verified). Marked failure of vision, somewhat improved temporarily by high voltage therapy. Partial removal of chromophobe adenoma, followed by further improvement in left field.*

A. A., a woman, aged 48, a housewife, was referred by Dr. M. Beigelman, Los Angeles, on July 11, 1930. For five months previously she had noticed blurring vision, which was greater in the right eye than in the left. Headaches, while not a prominent symptom at first, had been increasing. Visual fields, taken by Dr. Beigelman, showed slight bitemporal contraction. She was given a course of high voltage therapy elsewhere, but gradually her vision became worse. She again came under our observation on April 30, 1931, at which time there was a

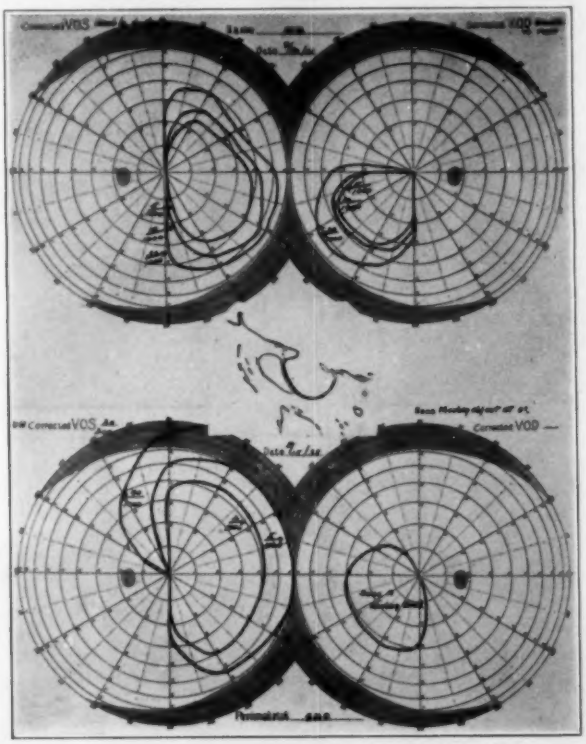

Fig. 8 (case 8).—Chromophobe adenoma (verified). Above are the visual fields before irradiation or surgical intervention and below, the fields two years after partial removal of the tumor and high voltage therapy. The insert shows the enlarged sella turcica, with almost entire destruction of the posterior clinoid processes and invasion of the posterior half of the sphenoid sinuses.

temporal hemianopia on the left and only an island of sight remaining in the right lower nasal quadrant (fig. 8).

Examination revealed a woman about 5 feet (152 cm.) tall, weighing 127 pounds (57.6 Kg.). She showed typical signs of hypopituitary disturbances. The skin was dry, the eyebrows scanty; distribution of hair over the body was practically lacking, and there were no lunulae on the nails except on the thumbs. The eyegrounds showed a primary optic atrophy on each side, with sharply outlined

disks, but fairly full arteries and veins. The neurologic examination revealed nothing of importance. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed practical obliteration of the posterior clinoid processes, with depression of the floor of the sella turcica into the sphenoid cavity, so that the latter was almost absent. The sellar cavity was greatly enlarged, about five or six times its normal size (fig. 8).

The fields improved appreciably following a course of high voltage therapy given elsewhere, reaching their maximum about July 6, at which time a bitemporal hemianopia existed. More than this was never attained. Following a further moderate course of high voltage treatment the fields failed to improve, and on November 19, six weeks after the last treatment, an exploratory operation was performed. A chromophobe adenoma was found and partially removed. The wound healed by first intention, but after ten days or two weeks it broke down in places, and subsequent healing was slow.

Comment.—This patient had had an indeterminate amount of irradiation elsewhere, prior to coming to us. She had some loss of hair. During August and September 1931, she was given twenty doses of 150 r. The intervals were irregular owing to severe headaches and the patient's inability to come to the laboratory. Following the partial removal of the adenoma her vision again improved (fig. 8), and the improvement, while not as much as could be wished, remained stationary for more than two years. Surgical intervention in this case was more beneficial than high voltage irradiation.

CASE 9.—*Pituitary tumor; probable cystic chromophobe adenoma (unverified). Bitemporal hemianopia. Continued loss of vision in spite of irradiation. Surgical intervention refused.*

R. C. H., a man, aged 39, married, a bookkeeper, was referred by Dr. Carl Fisher, Los Angeles, on Sept. 13, 1930. Two years previously he began to have failing vision in the right eye. This increased. He did not know that there was failure of vision of the left eye until a bitemporal hemianopia was found by Dr. Fisher on September 1. The patient had never been subject to headaches. Visual fields taken on September 15 showed a bitemporal hemianopia with low acuity in the left eye (fig. 9).

Examination revealed a man 6 feet (182.8 cm.) tall, weighing 190 pounds. He showed practically no signs of pituitary disorders. There was a primary optic atrophy on each side, more marked on the right than on the left. The arteries were smaller on the right than on the left. The deep reflexes on the left were a little quicker than on the right, but otherwise neurologic examination revealed nothing relevant. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed an enlarged sella turcica, with the enlargement chiefly forward and downward. There was some thinning of the posterior clinoid processes. The sphenoid sinuses were clear, but narrower than normal (fig. 9).

The patient was given a course of high voltage therapy from September 18 to November 6, with slight temporary improvement, but by December 31 vision had again failed, so that one was unable to chart the left side accurately, and what vision remained on the right side appeared to be in the upper nasal quadrant (fig. 9). Exploration of the pituitary region was strongly urged, but was refused. The patient has not been seen since.

Comment.—The patient was treated with doses of 150 r three times a week for seven weeks, except for the third, when he did not receive a treatment. As no benefit was derived, it was felt that the tumor was cystic. An exploratory operation should, of course, be performed.

CASE 10.—*Pituitary tumor; probable cystic chromophobe adenoma (unverified). Hypopituitarism; atypical bitemporal hemianopia. Temporary improvement following high voltage therapy.*

O. J. O., a man, aged 40, married, a plumber, was admitted to the Los Angeles County General Hospital on Oct. 13, 1930. There was an indefinite history of

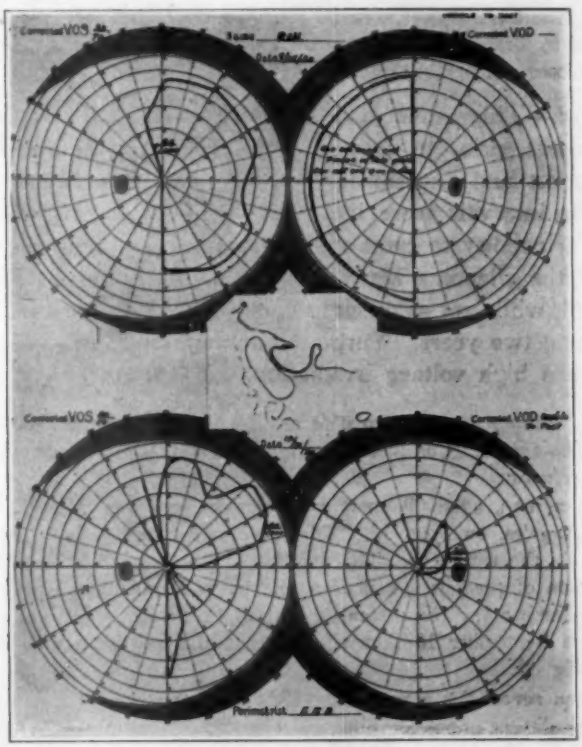

Fig. 9 (case 4).—Cystic chromophobe adenoma (unverified). Above are the perimetric fields when first seen, and below, the fields showing further loss of vision three months later following high voltage therapy. Surgical intervention was refused. The insert is a tracing of the sella turcica showing moderate enlargement of the structure with some clubbing of the posterior clinoid processes and no invasion of the sphenoid sinuses.

polyuria and polydipsia for many years. He drank about twelve glasses of water a day. Four years previously he began to have failing vision, more marked in the left eye. The visual fields, taken on December 16, show atypical bitemporal hemianopia (fig. 10). The patient had been having dull bitemporal and frontal headaches for several weeks previous to the examination.

Examination revealed a man with characteristics of abnormal function of the pituitary gland, about 5 feet, 10 inches (177 cm.) tall, weighing 164 pounds

(74.4 Kg.). The neurologic examination revealed no abnormalities. The eye-grounds showed sharply outlined, pale disks, with prominent optic cupping. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed the sella turcica to be about four times as large as normal. There was thinning of the floor, which dipped into the sphenoid sinuses. The posterior clinoid processes were thin, and the anterior clinoid processes were distinct (fig. 10)).

He was given high voltage irradiation elsewhere, consisting of insufficient weekly doses from December 1930 to June 1931, and again in November 1931 and in January 1932. The visual fields showed temporary improvement following the treatments and in April 1933 he was given a third course by Dr. Seeley Mudd at

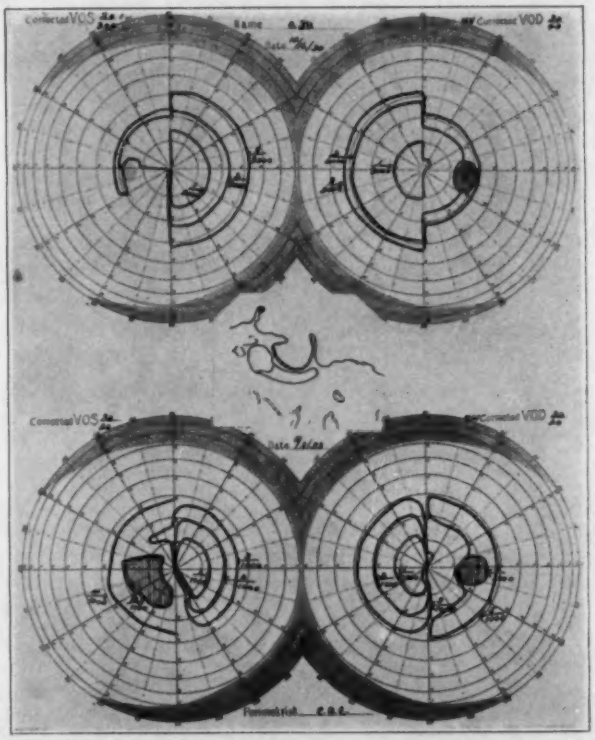

Fig. 10 (case 10).—Chromophobe adenoma (unverified). Above, the fields show the marked defect in the upper and lower temporal quadrants of each, and below is seen the condition of the fields three years later, following three courses of irradiation. The fields have fluctuated back and forth for three years, at times being considerably better than the fields shown below. Operation was refused. The insert shows the sella turcica with considerable thinning of the posterior clinoid processes and deepening of the floor of the sella turcica. The sphenoid sinuses are encroached on posteriorly.

the California Institute of Technology, at which time 600 kilovolts was used. Following this, there has been a little improvement in the fields (fig. 10). He has also had several mild petit mal attacks.

Comment.—This man should have an exploratory operation. Irradiation improved his vision only temporarily. The tumor may be a

cystic chromophobe adenoma. In spite of the fact that his vision has not materially improved in the past three years, during which time three courses of high voltage irradiation have been given, he has not lost ground. It is possible that irradiation retarded the growth of the tumor.

CASE 11.—*Pituitary tumor; probable chromophobe adenoma (unverified). Vision in right eye practically gone; temporal hemianopia in left eye. Slight improvement following high voltage therapy.*

M. E. F., a woman, aged 41, married, a housewife, was admitted to the Los Angeles County General Hospital on Aug. 24, 1929. There was a history of failing

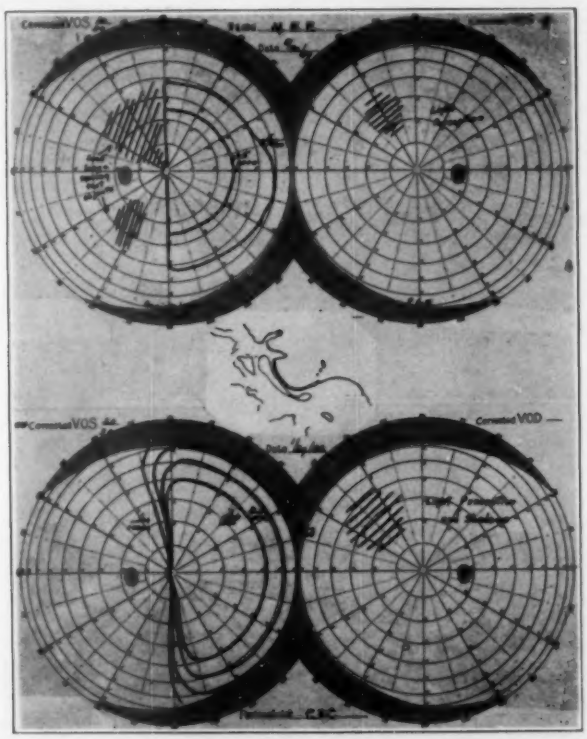

Fig. 11 (case 9).—Chromophobe adenoma (unverified). Above is shown the slight perception of light in the right upper nasal field and the fairly characteristic temporal hemianopia on the left; below the fields show practically the same condition on the right, with moderate improvement on the left three years later. Two courses of high voltage therapy were given, operation having been refused. The insert shows a tracing of an enlarged sella turcica, with almost total destruction of the posterior clinoid processes and marked invasion of the floor in the region of the sphenoid sinuses.

vision for three and a half years previously. Vision in the right eye was practically gone, and vision in the left was so poor that she could not read without using a reading-glass. The visual fields, taken on August 30, showed bare perception of light in the upper nasal quadrant of the right field and a temporal hemianopia of the left (fig. 11). She had never been subject to headaches.

Examination revealed a woman 5 feet, 5 inches tall, weighing 142 pounds (64.4 Kg.), showing no general evidence of disturbance of pituitary function. The eyegrounds showed a double primary optic atrophy and sharply outlined, pale disks. The disk on the right was considerably paler than that on the left. A general neurologic examination revealed no abnormalities. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed marked enlargement of the sella turcica, with ersion of the dorsum sellae. The posterior clinoid processes had practically disappeared, and the floor of the sella turcica was pushed down well into the sphenoid region (fig. 11).

She was given high voltage treatments elsewhere on October 5, 7 and 16. We are inclined to believe that they consisted of rather massive doses. We were unable to obtain reliable information regarding the exact amount of radiation or subsequent reaction. Following irradiation there have been fluctuations in the visual fields. A field taken on Jan. 29, 1932, showed moderate improvement (fig. 11).

Comment.—This patient has been advised repeatedly to have an exploratory operation, but has refused. It is possible that the adenoma has become cystic, as she had little benefit from intensive doses of irradiation.

CASE 12.—*Pituitary tumor; cystic chromophobe adenoma (verified). Bitemporal hemianopia; headaches. Temporary improvement following high voltage therapy. Later, partial removal of a cystic chromophobe adenoma.*

G. A. E. R., a woman, aged 44, married, a housewife, was admitted to the Los Angeles County General Hospital on April 30, 1931. She had been having severe frontal and occipital headaches for the previous two years, the principal pain being behind the eyes. Her weight had increased from 160 to 190 pounds (72.6 to 86.2 Kg.). The menopause had occurred eighteen months previously. There had been failing vision for seven months prior to examination, first noticed as a blurring of letters while reading. The left eye was affected more than the right. The failure of vision took the form of a bitemporal hemianopia, as shown by visual fields taken on May 1, 1931 (fig. 12).

Examination revealed a woman 5 feet, 6 inches (167.6 cm.) tall, weighing 190 pounds. There was tapering of the fingers and some coarsening of the skin, and hairy distribution over the body was becoming sparse. She showed typical primary optic atrophy of each eye, more marked on the right than on the left. The right pupil was larger than the left, but otherwise the neurologic examination gave negative results. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed a marked irregular enlargement of the sella turcica; the anterior clinoid processes were shortened; the posterior clinoid processes were almost completely eroded, and the floor of the sella turcica was irregular and flattened (fig. 12).

She was given a course of high voltage therapy elsewhere, consisting of four small weekly doses in June and July 1931 and a single dose in January 1932. Following this there was considerable improvement in the fields. The last record, taken on December 14, showed greater improvement in the left field than in the right; however, there was still a fairly atypical bitemporal hemianopia (fig. 12). Subsequently the fields became more contracted, and on May 13, 1932, a cystic chromophobe adenoma was partially removed at operation. The fields became normal, but after a year began to contract in the form of a bitemporal hemianopia.

The patient had also gained 35 pounds (15.9 Kg.), weighing, in June 1933, 225 pounds (102 Kg.).

Comment.—The recent gain of weight probably indicates an increase of the symptoms of hypopituitary disturbance caused by removal of tissue of the anterior lobe a year previously. Reexploration is being considered because of the return of (her) visual deterioration. Whether further removal of the adenoma will again increase the symptoms of glandular deficiency, already so marked, is an open question.

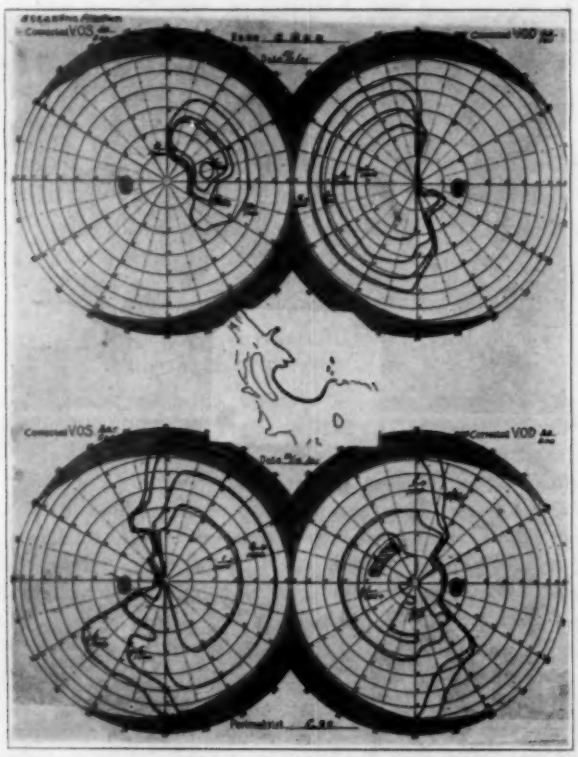

Fig. 12 (case 12).—Cystic chromophobe adenoma (verified). Above, the fields show the condition before high voltage therapy, and below, the improvement following two courses of high voltage therapy seven months later. Full restoration of the fields followed partial removal of the tumor, but a year later contraction again occurred. The insert shows the sella turcica greatly enlarged, with almost total destruction of the posterior clinoid processes and invasion and partial obliteration of the sphenoid sinuses.

CASE 13.—*Pituitary tumor; probable chromophil adenoma (unverified). Acromegaly; beginning constriction of visual fields. Improvement of fields following high voltage therapy. Subsequent decompression because of headache.*

A. B., a woman, aged 36, unmarried, a school-teacher, was referred by Dr. Philip M. Savage, San Bernardino, Calif., on Sept. 16, 1930. Her principal com-

plaint was pain in the back of the head, neck and shoulders, which had been present for the past five or six years. She had not noticed difficulty in vision, but the fields, taken on September 16, showed general contraction on both sides, the contraction being relatively greater in the temporal field than in the nasal (fig. 13).

Examination revealed a woman 5 feet 2 inches (157.4 cm.) tall, weighing 147 pounds (66.7 Kg.), who showed typical acromegalic changes in her features and extremities. Her hair was very heavy, dry and coarse. The amount of hairy distribution over the body was increased and was of the masculine type. Her hands and feet were large; the size of shoes had increased from 6¼ to 7¼ in the past few years. The eyegrounds showed nothing remarkable. The margins

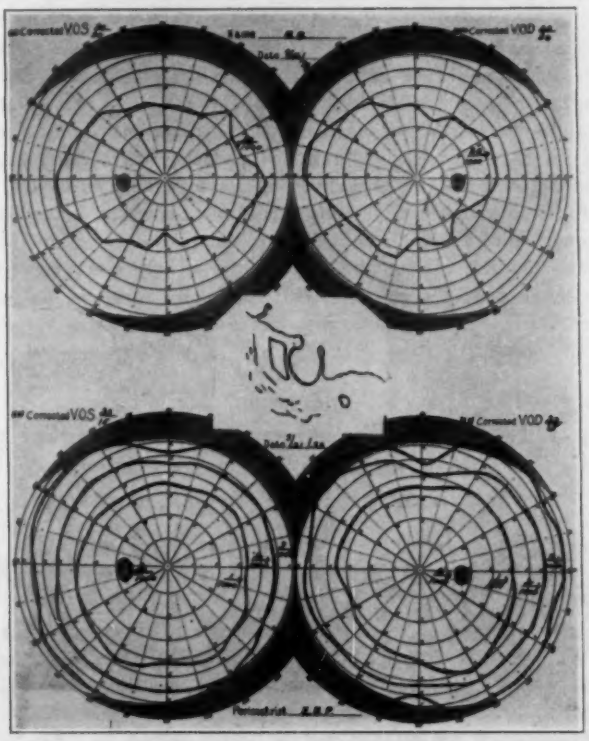

Fig. 13 (case 13).—Chromophil adenoma (unverified). Above are the fields before irradiation, and below, following two courses of high voltage therapy and subsequent subtemporal decompression. The insert shows the sella turcica moderately enlarged, deep and narrow, with thinning of the posterior clinoid processes and clubbing of the anterior clinoid processes. The sphenoid sinuses are definitely encroached on.

of the temporal disk were clear. The nasal margins were somewhat indistinct, and there was some overfilling of the veins. There was no pallor of the disks. Otherwise, the neurologic examination revealed no abnormalities. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed typical changes of acromegaly, with an unusually thick, dense calvarium. The mandible was heavy. There were enostoses of the frontal bone. The sella turcica

was very large, the major enlargement being downward toward the sphenoid sinuses. The posterior clinoid processes were very thin, but not displaced. The floor of the sella turcica appeared to be intact (fig. 13). Roentgenograms of both hands failed to show tufting of the terminal phalanges.

She was given a course of high voltage therapy consisting of doses of 150 r five times a week during September 1930, with marked improvement in the visual fields. Following this, there was an increase of her headaches. This continued during the following year. From July 2 to July 20, 1932, she was given a similar course of 150 r daily for eighteen days, not because of constriction of the visual fields, but because of headache. Fields taken after this (fig. 13) remained essentially normal. The headaches continued, and on August 22, a simple right subtemporal decompression was carried out. The tissues were unusually vascular, although the intracranial pressure was not increased. It was felt that the vascularity of the tissues might be secondary to the last course of irradiation, which was completed less than five weeks before the operation. The sellar region was not examined, as there were no neighborhood signs of pressure. She returned to her teaching duties, and reported that the headaches were in no way improved. Although she presented no neighborhood symptoms, the continuance of headache may in the future lead us to explore the chiasm. Should a distended diaphragma sellae be found, relief from distention might be followed by an improvement in the headaches. On the other hand, many patients with acromegaly have been reported who have gone through life with continued headache, although they did not otherwise show signs of generally increased intracranial tension or undue pressure on the chiasm.

Comment.—This patient underwent both courses of treatment exceedingly well; the doses, though small, were given more rapidly and more steadily than in most cases of the series. The acromegalic features of the case have not increased during the past two years.

CASE 14.—*Pituitary tumor; chromophobe adenoma (verified). Bitemporal hemianopia, with improvement following high voltage therapy. Death due to cerebral hemorrhage.*

P. E. E., a man, aged 68, married, an agricultural inspector, was referred by Dr. C. B. Walker, Los Angeles, on Sept. 27, 1930. His only complaint was failing vision, which had first been observed eighteen months previously. This was called to his attention while doing fine printing. By July 1930 he was unable to pass an examination for his automobile license owing to difficulty in reading. Visual fields taken on September 27 by Dr. C. B. Walker (fig. 14) showed a fairly typical bitemporal hemianopia, more advanced on the right than on the left. He did not complain of headache at any time.

Examination revealed an elderly man 5 feet, 7 inches tall, weighing 144 pounds (65.3 Kg.). He showed slight evidence of hypopituitary disturbance. His beard was very light, and the hairy distribution over the body was scant. There were no lunulae of the fingernails. The eyegrounds showed both disks to be sharply outlined and a little paler than normal. The lamina cribrosa was distinct. The right disk was paler than the left. The neurologic examination gave negative results. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed enlargement of the sella turcica, with almost complete absorption of the clinoid processes. Several shadows were seen which were suggestive of a cyst wall (fig. 14).

The patient was given a course of high voltage therapy consisting of doses of 150 r three times a week for six weeks, ending November 14, with marked improvement in his visual fields, as shown by Dr. Walker's chart taken on Feb. 17, 1931 (fig. 14). He returned to work, and apparently was in good health, until one year later, when he died of a cerebral hemorrhage on Dec. 24, 1931.

A report of the autopsy, performed by Dr. G. D. Maner, contained the following: On reflecting back the cerebrum after incising the dura, there was found an irregular lobulated mass located beneath the dura and occupying the sella turcica. The optic chiasm lay just anterior to it, and was greatly elongated and distorted, especially the left fork; the posterior portion lying over the tumor was

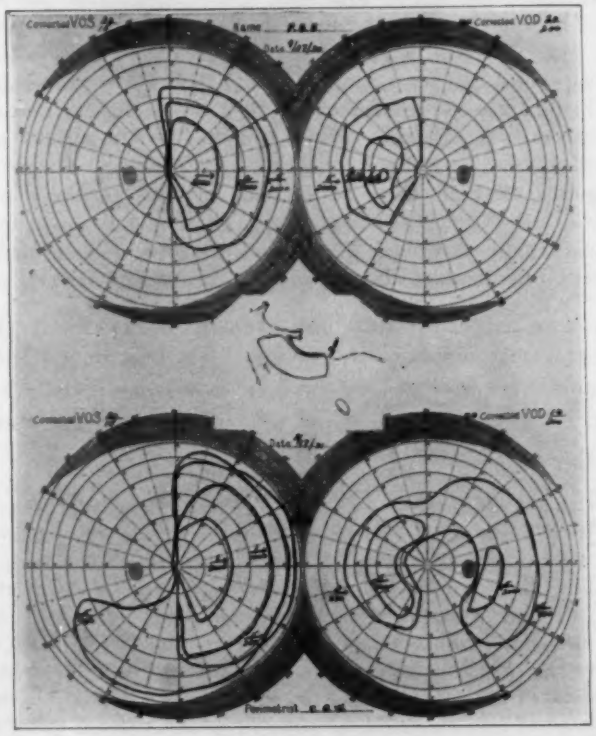

Fig. 14 (case 14).—Chromophobe adenoma (verified). Above, the fields show marked constriction in the form of a bitemporal hemianopia before irradiation, and below, definite improvement six months later. The insert of the sella turcica shows almost complete destruction of the posterior clinoid processes and marked blunting of the anterior clinoid processes. The shallow type of sella turcica shows little, if any, invasion of the sphenoid region.

greatly widened. There was a concavity on the inferior surface of the cerebrum, between the peduncles and the chiasm, which conformed to the shape of the tumor. Both ophthalmic arteries, as well as the third, fourth and sixth cranial nerves on both sides were elongated, widened, distorted and displaced laterally.

The tumor involved the whole of the hypophysis and weighed 18.5 Gm. Its measurements were: width, 5 cm.; anterior posterior diameter, 4 cm., and greatest thickness, 3 cm. It was roughly bilobed, with the right lobe approximately twice

the size of the other. The overlying dura was intact. The surface was smooth, but the greater part of the anterosuperior aspect was blood stained. The consistency was liver-like, but the hemorrhagic portions were softer. The sectioned surface was smooth; the greater part was a dull, gray-pink, but along the anterior portion and on the whole length of the right lobe was an area of diffuse hemorrhagic extravasation.

The sella turcica was greatly widened in all dimensions; the normal contour was missing, the outline being perfectly flat. The dimensions were: length, 4 cm.; width, 3.75 cm. The floor was intact and the sphenoid cells were of normal outline. The posterior and anterior clinoid processes were absorbed.

On microscopic examination the sections showed an anterior lobe struma. The follicles were greatly increased in number; many were small, but others were of normal size. Practically all were compact and filled with chief, or chromophobe, cells, with only an occasional eosinophil cell. The cells were rounded or short cylindric. The follicles were surrounded by thin septums of connective tissue containing thin-walled capillaries. These appeared to be normal, as compared with a normal gland. No histologic evidences of a malignant process were found.

The diagnosis was: chromophobe adenoma of the pituitary gland; cerebral arteriosclerosis, and recent hemorrhage in the left temporal lobe of the brain.

"No changes in the histologic picture were seen to suggest that irradiation had any effect on the tumor in the way of interstitial or cellular changes."

Comment.—In this instance improvement to serviceable vision was obtained in a chromophobe adenoma. The accidental death from apoplexy more than a year later gave an excellent opportunity to study the pituitary gland. No histologic changes were found at this late date which could be ascribed to irradiation.

CASE 15.—*Pituitary tumor; probable chromophobe adenoma (unverified). Bitemporal hemianopia. Improvement in fields following high voltage therapy.*

J. F. K., a man, aged 47, married, a barber, was referred by Dr. J. Ross Reed, Pasadena, Calif., on Dec. 26, 1930, with a diagnosis of tumor of the pituitary gland. For ten years previously there had been some difficulty in seeing with the left eye, and about five months previously he noticed failing vision in the right eye. He now had difficulty in seeing well enough to cut hair or shave patrons. A visual field taken on December 26 (fig. 15) showed a typical bitemporal hemianopia, with marked constriction of the nasal fields and lowered visual acuity. He had not complained of headache at any time.

Examination revealed a man 6 feet tall, weighing 200 pounds (90.7 Kg.). He showed definite characteristics of hypopituitary disturbance, such as dryness of the skin and scantiness of hair over the face and body. Although a large man, he did not appear to be acromegalic. The eyegrounds showed the margins of the disks to be indistinct, with overfilling of the veins, but no measurable elevation. The disks seemed somewhat paler than normal. It was not a clearcut picture of primary optic atrophy. The right pupil was larger than the left, but the neurologic examination was otherwise irrelevant. The Wassermann reaction of the blood was negative. Roentgenograms of the skull, taken on December 26, revealed a definite enlargement of the sella turcica, with practically a loss of the posterior clinoid processes. The floor of the sella turcica was depressed toward the sphenoid bone. It was difficult to get a clear view of the pituitary gland, because of massive mastoid cells (fig. 15).

The patient was given a course of high voltage therapy consisting of doses of 150 r three times a week for two and a half weeks, ending Jan. 14, 1931, and a similar course from March 20 to April 7, with considerable improvement in the fields. The man had a head of a large diameter, and the amount of dosage delivered at the tumor was smaller than the average. The last field, taken on Oct. 25, 1932, approximately two years later, still showed a hemianopia on the right, but enlargement of the fields in both the upper and the lower temporal quadrants on the left. The visual acuity was unchanged.

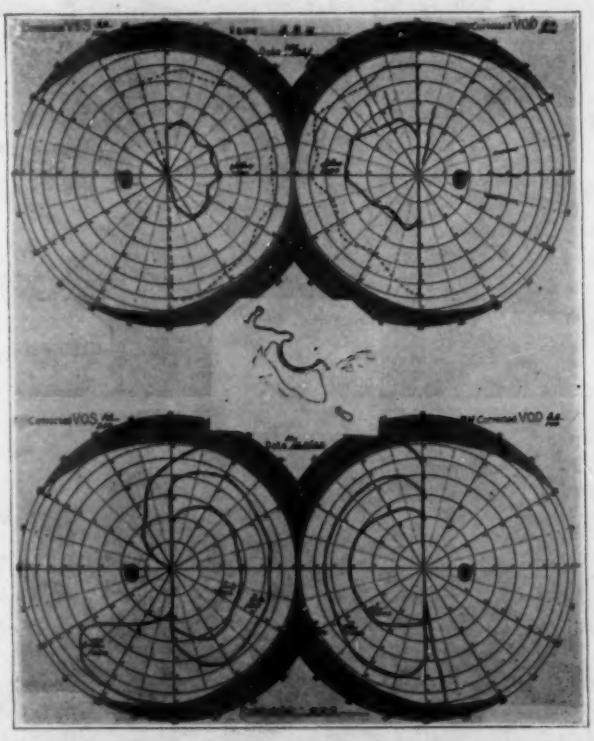

Fig. 15 (case 15).—Chromophobe adenoma (unverified). Above is seen the marked contraction of both fields in the form of a bitemporal hemianopia before irradiation, and below, the improvement two years later, following two courses of high voltage therapy. The insert shows the sella turcica which was moderately enlarged, with almost complete destruction of the posterior clinoid processes and moderate invasion of the sphenoid sinuses.

Comment.—This patient later moved to Oakland, Calif., and is under the care of Dr. Howard C. Naffziger, San Francisco, who reported on May 22, 1932, that "his fields are purely those of a bitemporal hemianopia at present." Dr. Naffziger determined to keep the patient under monthly observation, and if his acuity or field decreased to advise an operation. The patient undoubtedly had an insufficient amount

of irradiation while under our observation; if the dosage had been more intensive and additional courses given, further improvement might have been obtained.

CASE 16.—*Pituitary tumor; probable chromophobe adenoma (unverified). Marked headaches and bitemporal hemianopia; improvement of both following high voltage irradiation.*

E. H. G., a man, aged 42, married, an automobile mechanic, was referred by Dr. H. L. Hatfield, Pasadena, Calif., on May 20, 1931. He had been complaining of failing vision for four or five years previously, and a bitemporal hemianopia

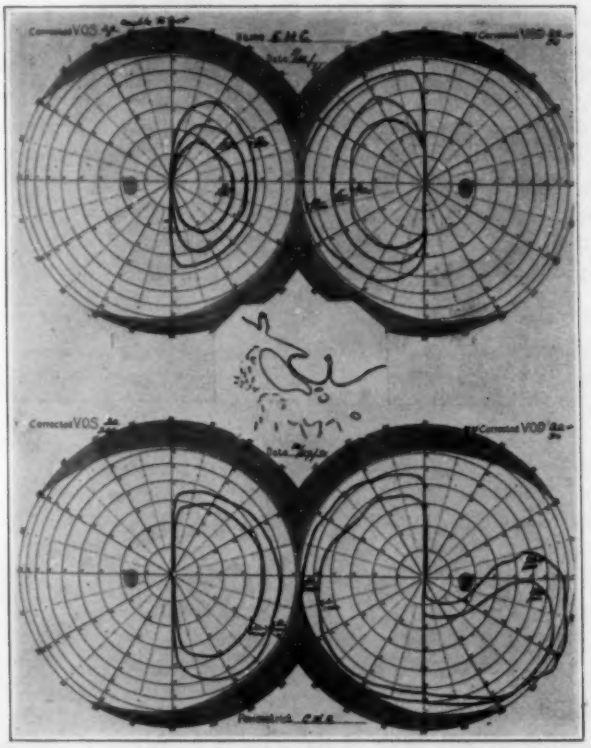

Fig. 16 (case 16).—Chromophobe adenoma (unverified). Above is seen a bitemporal hemianopia with marked contraction of the temporal fields on the left prior to irradiation, and below, the improvement six months later, especially on the right, following two courses of high voltage therapy. The insert is a tracing of the sella turcica showing moderate enlargement, with thinning of the anterior and posterior clinoid processes. The sphenoid sinuses are moderately narrowed posteriorly.

had developed two years previously. Vision in the left eye was more impaired than that in the right, as shown by the visual field taken on May 26 (fig. 16).

Examination revealed a medium-sized man. For ten days previous to the examination he had had severe headaches, accompanied by nausea and vomiting.

The headaches were improved and nausea and vomiting ceased following the administration of hypertonic solution of dextrose intravenously. The left disk was sharply outlined and very pale; the right disk was hazy, the veins were congested, a fresh hemorrhage was present in the upper temporal quadrant, and the disk itself was somewhat paler than normal. The right knee jerk was quicker than the left, and there was a positive and well sustained ankle clonus on the right side. Otherwise the neurologic examination gave negative results. The Wassermann reaction of the blood was negative. Roentgenologic examination of the skull showed a much thinned, considerably enlarged sella turcica, about twice the normal size. The posterior clinoid processes were present, but greatly thinned; the floor of the sella turcica encroached on the sphenoid sinuses (fig. 16).

The patient was given two courses of high voltage therapy consisting of average daily doses of 145 r for two weeks, and six weeks later a similar course, by Dr. Carl H. Parker, Pasadena, with marked improvement in the fields, as shown by the record made on October 27 (fig. 16).

Comment.—This man was bedridden when first seen, having severe headaches and projectile vomiting. An exploration of the pituitary region was advised, but was refused. Although we feared there would be a serious reaction, he was given high voltage therapy. Previous to irradiation he was dehydrated, and hypertonic solution of dextrose was given intravenously. No reaction followed the irradiation. Whether the dehydration was a factor in this is speculative. Radiation was given more rapidly and intensively than in any other case in the series, with marked improvement of the fields more than five months later (fig. 16). Three years later he was at work, with serviceable vision and complete relief from the headaches.

CASE 17.—*Pituitary tumor; probable chromophobe adenoma (unverified). Marked enlargement of sella turcica; bitemporal hemianopia; hypopituitarism. Considerable improvement in visual fields following two courses of high voltage therapy.*

L. T., a man, aged 39, in the furniture business, was referred by Dr. J. M. Schmoele, Los Angeles, on Oct. 1, 1931. There was a history of failing vision for about a year previously, both eyes being affected, but the left more than the right. The visual fields, on first examination, showed a typical bitemporal hemianopia. The left field showed more loss than the right. Visual acuity was: left, 20/200; right, 20/40 (fig. 17). He also gave a history of previous headaches which at times were severe and accompanied by nausea and vomiting. He had a typical syndrome of hypopituitary disturbance, with loss of libido and a tendency to be drowsy and to tire easily. He also showed fairly characteristic changes in the skin.

Examination revealed a man with typical signs of hypopituitary disturbance; he was of medium size and build, with a soft, dry skin and a scarcity of hair as regards the beard and other parts of the body. There was bilateral primary optic atrophy with sharp-cut disks, which were only moderately pale. The retinal arteries and veins were of good caliber. The general neurologic examination revealed no abnormalities. The Wassermann reaction was negative. Roentgeno-

grams of the skull showed a somewhat enlarged sella turcica with fairly normal anterior clinoid processes; the posterior clinoid processes were practically destroyed, the shadow of only one being definitely made out. The floor of the sella turcica was not particularly depressed (fig. 17).

Comment.—The patient was given two courses of high voltage therapy, the first of 150 r every second day covering two weeks, ending Oct. 23, 1931, and the second a similar course ending March 20, 1932. The doses were small, the courses short and the total amount

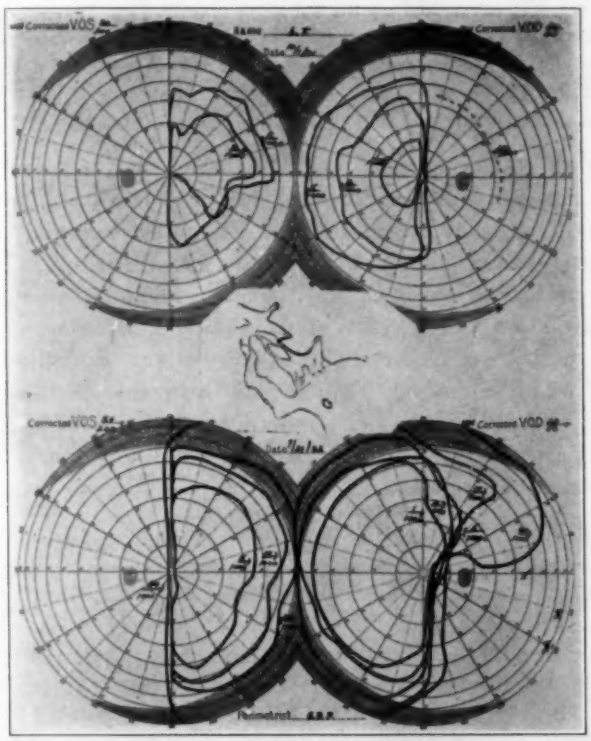

Fig. 17 (case 17).—Chromophobe adenoma (unverified). Above, the fields show the typical bitemporal hemianopia before high voltage treatment, and below, improvement in the fields approximately one year later, following two courses of high voltage therapy. The insert shows the sellar region, with the sella turcica but little enlarged and fragmentation of the posterior clinoid processes. The sphenoid sinuses are a peculiar multiloculated type.

unsatisfactory. Following the high voltage therapy he had a fluctuating course. On the whole, there was improvement in the fields (fig. 17). At times, however, they regressed considerably. He adopted Christian science, and did not report after Dec. 12, 1932. An exploratory operation should probably be carried out.

CASE 18.—*Pituitary tumor; probable chromophil adenoma (unverified). Acromegaly. Vision of right eye confined to upper nasal quadrant. Practically blind in left eye. Unsuccessful attempt to remove tumor; decompression. Marked improvement of vision following high voltage therapy.*

E. L. B., a man, aged 44, married, district manager for an electric company, was referred by Dr. F. X. Ammann Jr., Los Angeles, on Oct. 3, 1931. Four years previously he began to have failing vision and violent headaches. A Wassermann reaction of the blood at that time was 4 plus. He improved under antisyphilitic treatment, as to both headaches and vision. One year ago his vision began to fail, and the failure progressed rapidly. On October 6 the visual fields (fig. 18) showed an area of vision in the upper nasal quadrant of the right eye, the left being practically blind. He was having violent headaches at this time.

Examination revealed a man 6 feet tall, weighing 200 pounds, who was definitely acromegalic. The eyegrounds showed both disks to be very pale and sharply outlined. Atrophy on the left side was greater than on the right. The veins were large, but the arteries were exceedingly small. The left pupil did not react to light. The right reacted sluggishly. Otherwise, the neurologic examination revealed no abnormalities. Roentgenograms of the skull showed an enlargement of the sella turcica, with almost complete destruction of the posterior clinoid processes. There was encroachment of the floor of the sella turcica into the sphenoid region (fig. 18).

On October 18, an attempt was made to explore the pituitary gland by a right frontal approach. The brain was under tremendous tension; the right ventricle was apparently collapsed, and it was impossible to secure sufficient room to uncover the chiasm satisfactorily. A decompression of liberal size was performed, and high voltage therapy was instituted two weeks later. The patient has had two courses of irradiation, with marked improvement in the fields and in acuity. This is the only case in which vision returned in a practically blind eye. Fields taken on May 23, 1933 (fig. 18), show that acuity in the left eye is 20/40, and the left field is essentially normal; acuity in the right eye is 20/30 and the field has filled out except for a defect in the lower temporal quadrant.

Comment.—The patient had an exploratory operation with decompression before treatment was started, and as a result, a larger dosage, given more rapidly, was possible. He was treated nearly continuously each day for four weeks, with 200 r at each dose. No treatment was given then for five weeks, at which time he was given a second similar course for three weeks. He had no unpleasant reaction.

During October 1933, he began again to show slight constriction of the temporal fields. Consequently, it was considered advisable to give another course of high voltage irradiation. Twelve treatments of 300 r each were given every other day between October 26 and November 20, without disagreeable reaction except for a slight headache following the first two treatments. The decompression area is growing smaller, and apparently new bone proliferation is taking place along the edges of the defect. This may in some way be associated with the acromegaly, and the argument could be used that the acromegaly is advancing.

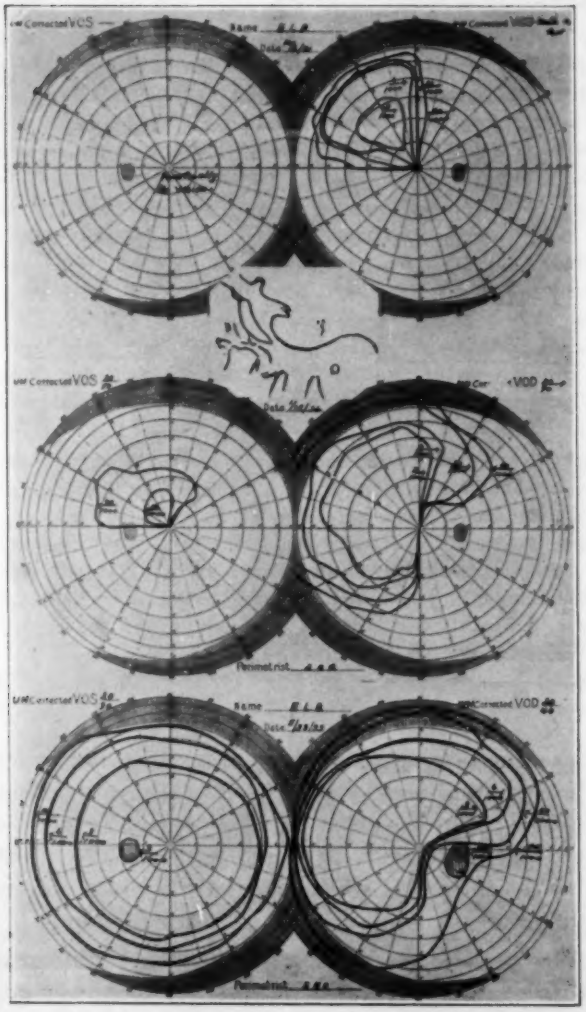

Fig. 18 (case 18).—Chromophil adenoma (unverified). The upper charts show vision remaining in the upper nasal quadrant in the right eye, with practically no vision in the left eye, before decompression followed by high voltage therapy. The middle chart shows improvement three months later in the right field and beginning return of vision in the left upper temporal and nasal quadrants. The lower chart shows further improvement in the fields which still obtained two years later. The insert shows enlargement of the sella turcica, with almost complete destruction of the posterior clinoid processes and invasion of the floor of the sella turcica into the region of the sphenoid sinuses.

CASE 19.—*Pituitary tumor; probable chromophobe adenoma (unverified). Atypical hemianopic defect of visual fields. Headaches. Considerable improvement in right eye; continued loss of vision in the left eye following two courses of high voltage therapy.*

N. L. A., a man, aged 49, a farmer, was referred by Dr. Charles A. Lindquist, West Los Angeles, on Feb. 3, 1932. His principal complaint was failing vision for the previous five years. This was increasing. Repeated change of glasses had failed to improve his vision. Three years previously he began to have bitemporal headaches, which had continued. At times they were severe, giving him a sense

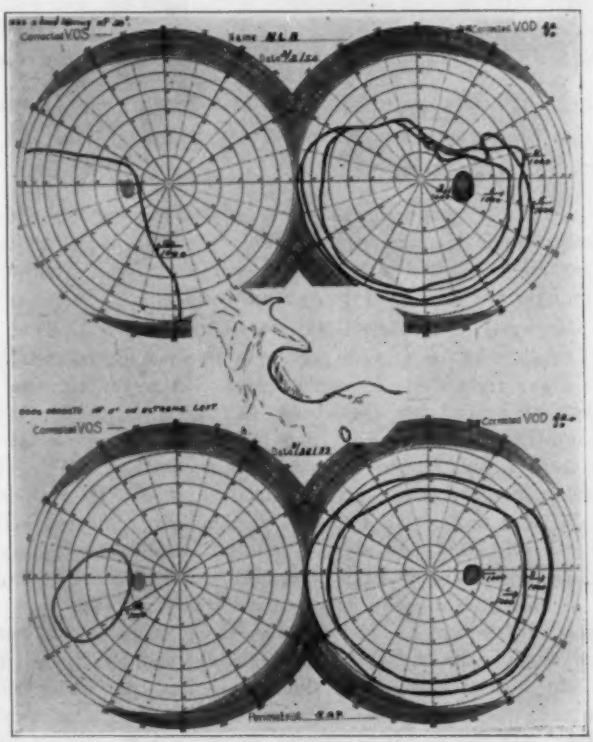

Fig. 19 (case 19).—Chromophobe adenoma (unverified). Above are the visual fields before irradiation; below, the fields one year after irradiation. Vision on the right has definitely improved, and on the left has failed. The insert shows an enormous sella turcica, with complete obliteration of the posterior clinoid processes; the floor of the sella invades the sphenoid sinuses.

as though the left eyeball were being pushed down. During the severe headaches, the vision was much worse.

Examination revealed a man, 6 feet tall, weighing 225 pounds. His father, mother, two brothers and one sister were large. He showed no acromegalic tendency. The eyegrounds showed a double primary optic atrophy, with sharply outlined disks which were definitely pale. The atrophy of the left disk was more marked than that of the right. The veins were of average size, the arteries small.

The visual fields showed an upper nasal and temporal defect of the right eye and a large lower temporal defect of the left eye. The visual acuity on the right was 20/40, and on the left so poor that he could see only movements of the hand at 20 feet (6 meters) and the largest disk, 40 mm., at 1 meter (fig. 19). The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed an enormous enlargement of the sella turcica. It was 3.5 cm. from the anterior clinoid processes to the posterior wall of the cavity. The posterior clinoid processes had disappeared. The floor of the sella turcica was absorbed or pushed down so far that the sphenoid sinus was obliterated (fig. 19).

He was given a course of irradiation consisting of daily doses of 150 r for twenty-five days, with marked improvement in the right eye, but without improvement in the left. In fact, the vision in the left eye gradually failed. The fields (fig. 19) show the changes which occurred over a period of fifteen months.

Comment.—This patient should have further irradiation and, if necessary, an exploration of the pituitary gland. It is not impossible that the tumor is becoming cystic.

CASE 20.—*Pituitary tumor; probable chromophobe adenoma (grossly described as "a gliomatous tumor" by the coroner). Enlargement of sella turcica. Temporal hemianopia on left and loss of useful vision on right. No improvement following one course of high voltage therapy. Sudden death.*

O. R., a man, aged 32, a laborer, was referred on March 22, 1932, by Dr. John N. Osburn, Los Angeles. Six years previously he first noticed difficulty in seeing. This began in the right eye. It was called to his attention when sighting his gun while hunting. Gradually the visual difficulties increased. At the time of our first examination, vision in the right eye was reduced almost to shadows. On the left there was a typical temporal hemianopia (fig. 20). There was no history of severe headaches, although at times there had been moderate pain in the back of the head and neck. This was particularly true four years previously.

Examination revealed a man about 5 feet, 7 inches tall, weighing 204 pounds (92.5 Kg.). He showed no general characteristics of pituitary dysfunction. The eyegrounds revealed both disks to be sharply outlined and very pale. In fact, the right disk was chalky white. The veins were of average size, but the retinal arteries were much reduced. The neurologic examination revealed nothing of importance. Roentgenograms of the skull showed no particular enlargement of the sella turcica; the floor, however, was depressed, dipping almost into the sphenoid cavity, and the posterior clinoid processes were practically obliterated (fig. 20).

On March 15, at the California Institute of Technology, he had been given one exposure of 600 kilovolt radiation, of 300 r units, delivered in the right temporal region. He failed to return for further treatment. When first seen by one of us (C. W. R.), he was urged to have an exploration of the pituitary gland because of rapid loss of vision. This he refused to permit. He was then given a course of high voltage irradiation, which consisted of ten 200 r treatments, from April 21 to May 11. There was no appreciable improvement in the fields (fig. 20).

He returned to work as a laborer, most of the work being done in a tunnel where a dam was being constructed. According to his physician, one day he became suddenly ill. This was followed by two or three days of acute headache and vomiting; then he suddenly died, on March 30, 1933. The brain was examined by the coroner who reported: "a gliomatous tumor the size of an egg at the base of the brain, partly occupying the sella turcica." This was beyond question a

large pituitary adenoma, probably of the chromophobe variety. Unfortunately, the tissue was not saved for microscopic examination.

Comment.—The single treatment of 300 r probably had no appreciable influence on the pituitary gland. The course of treatments given by us was comparable in dosage with that given in the other cases of the series. Following it there was no improvement in his vision. Only nineteen days elapsed from the time of the last treatment until his death. This was hardly sufficient time to state whether improvement might

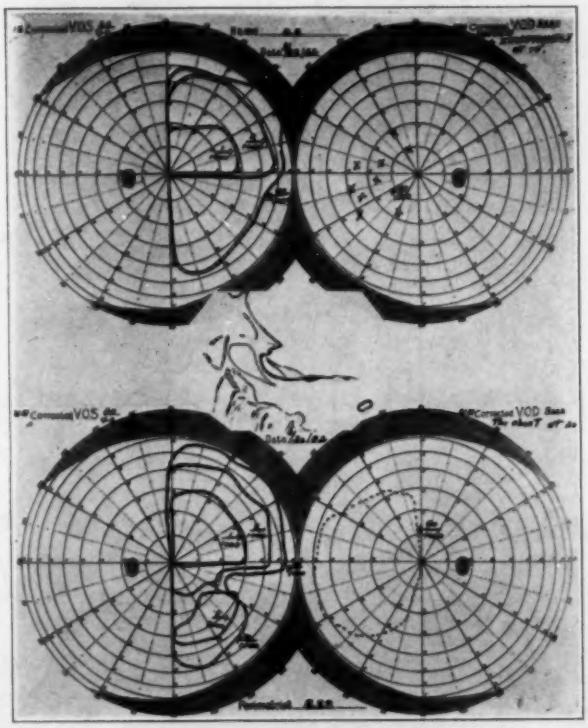

Fig. 20 (case 20).—Chromophobe adenoma (grossly verified). Above are the visual fields before irradiation, showing vision on the right almost gone except for large objects in the nasal field, and below, the absence of improvement of vision two months after one course of irradiation. Operation was refused. The insert shows almost complete destruction of the posterior clinoid processes and invasion of the posterior half of the sphenoid sinuses.

have occurred later. The coroner's report did not tell whether the tumor, as found at autopsy, was cystic or not.

CASE 21.—*Pituitary tumor; cystic chromophobe adenoma (verified). Bitemporal hemianopia; headaches; amenorrhea. Continued failure of vision following high voltage therapy. Partial removal of cystic chromophobe adenoma, with return of fields to normal.*

A. R., a woman, aged 30, unmarried, a nurse, was referred by Dr. E. C. Jeançon, Los Angeles, on April 19, 1933. Menstruation was established at the age of 13, but amenorrhea developed at the age of 21. About March 1933 she first noticed blurring of the vision, which was soon followed by bitemporal headaches and

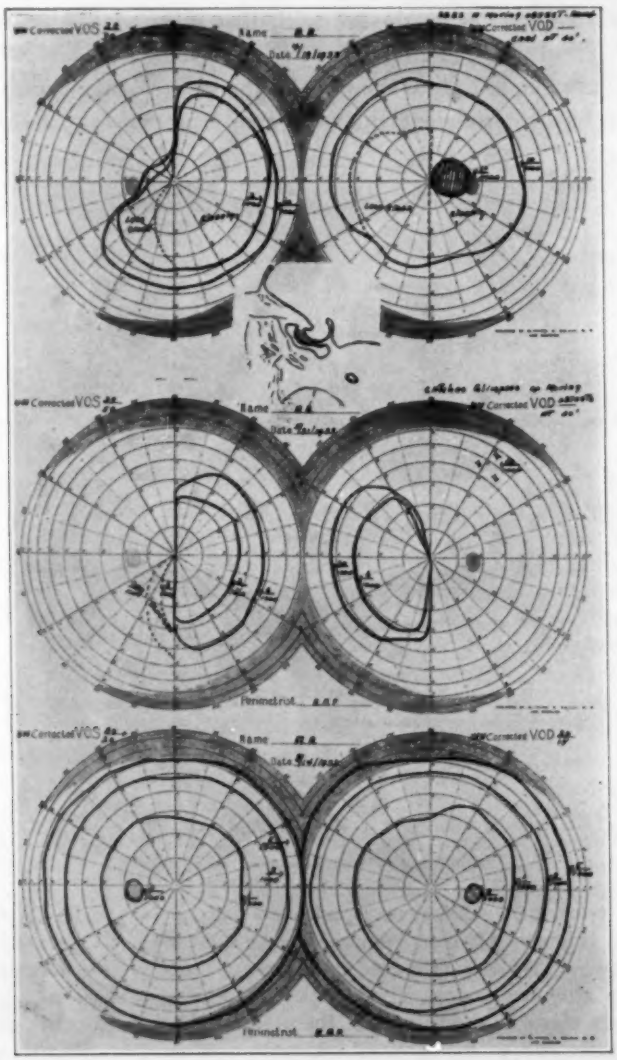

Fig. 21 (case 21).—Cystic chromophobe adenoma (verified). The upper chart shows the condition of the fields when first seen, before high voltage therapy or surgical intervention had been instituted. The center chart shows the advanced constriction following adequate high voltage therapy, and the lower chart reveals the return of the fields and acuity to normal in both eyes following evacuation of a cyst and partial removal of a tumor. The insert shows a moderately enlarged sella turcica, with little, if any, erosion of the anterior or posterior clinoid processes. There is some invasion of the sphenoid sinuses.

occasional dizziness. The visual fields, on April 19, showed considerable contraction on the right, with enlargement of the blind spot and greatly lowered acuity, together with marked temporal constriction on the left, especially in the upper quadrant (fig. 21).

Examination revealed a woman about 5 feet, 8 inches (172.7 cm.) tall, weighing 172 pounds (78 Kg.), who showed rather definite tendencies toward obesity. She had mild symptoms of hypopituitary disturbance. The eyegrounds showed definite pallor of both disks, but the general neurologic examination revealed no abnormality. The Wassermann reaction of the blood was negative. Roentgenograms of the skull showed only moderate enlargement of the sella turcica. The posterior clinoid processes, however, were thinned and eroded, and there was some encroachment of the floor of the sella turcica on the sphenoid sinuses (fig. 21).

She was given 120 r doses through each of three ports, daily for eight days. These were repeated on the third, eighth and twelfth subsequent days, the whole period being about three weeks. Marked erythema developed in one area. Nevertheless, her vision continued to fail rapidly, so that she soon showed a typical bitemporal hemianopia. On the right, the acuity was so low that she could only see moving objects; on the left, 20/50 (fig. 21). An exploratory operation was performed on June 3, at which time a large cystic chromophobe tumor of the pituitary gland was found and emptied. The pathologic diagnosis was cystic chromophobe adenoma. Following partial hypophysectomy the fields began to improve rapidly, and by August 14 had returned to normal.

Comment.—This patient was given doses of high voltage irradiation in rapid succession. However, the visual symptoms became more alarming, and an exploratory operation seemed imperative within three weeks of the beginning of treatment. A typical cystic chromophobe adenoma was encountered, following the evacuation of which she made satisfactory progress. She is still amenorrheic. This case bears out the contention that cystic adenomas do not react favorably to high voltage therapy, but respond well surgically. In this case the surgeon feared difficulty from hemorrhage as a result of the recent treatment, but was gratified to find that nothing of the sort occurred.

CASE 22.—*Pituitary tumor; probable chromophil adenoma (unverified). Marked contraction of both fields with bitemporal hemianopic defect predominating. Improvement following high voltage irradiation.*

L. B., a woman, aged 27, married, a housewife, was referred by Dr. Fred S. Modern, Los Angeles, on June 29, 1933. For about a year she had been subject to headaches which were principally bitemporal or frontal. Blurring vision began approximately a year previously, but had increased rapidly during the previous two months. The fields, taken on June 29, showed marked contraction on both sides, with a greater defect in the temporal than in the nasal area (fig. 22). The physical examination revealed nothing suggestive of disease of the pituitary gland except a mild acromegalic look. The nose and lips were full; the general build was rather masculine, and the texture of the skin coarse. The patient had no menstrual disorders. The neurologic examination gave negative results. The eyegrounds showed a well established primary optic atrophy, present on each side. Roentgenograms of the skull showed a definitely enlarged sella turcica, with thinning of the posterior clinoid processes and moderate encroachment of the floor of the sella turcica on the sphenoid sinuses (fig. 22).

A course of high voltage therapy was given which consisted of a series of fifteen doses of 200 r administered almost daily, beginning on June 30 and ending July 16. During the treatment the patient's headaches, if anything, were increased, but not enough to reduce the treatments. She began to notice improvement of her vision within three weeks after high voltage irradiation was started. Figure 22 shows the degree of improvement of the fields on October 30.

Comment.—This would appear to be a case of early acromegaly with moderate enlargement of the sella turcica and beginning visual dis-

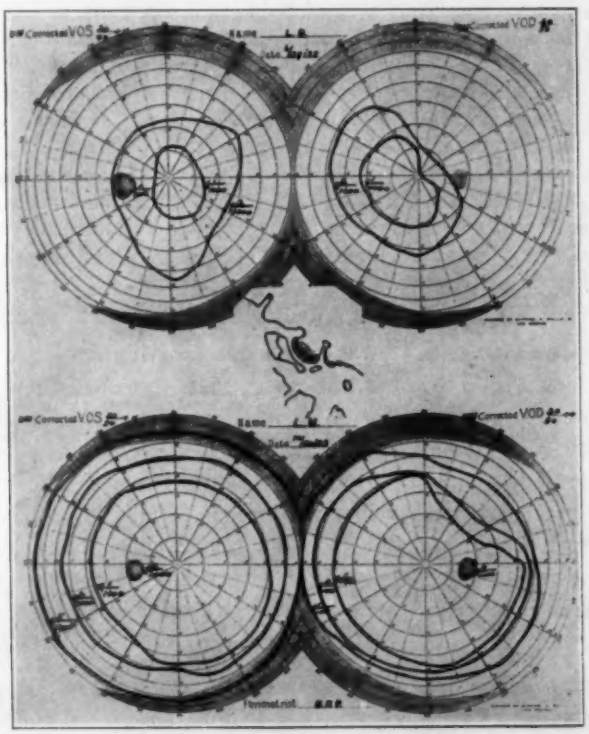

Fig. 22 (case 22).—Chromophil adenoma. Above are the fields taken before irradiation, showing the somewhat bizarre and advanced contraction tending toward a bitemporal hemianopia; below, the fields have returned to normal practically following irradiation. The insert shows a moderate enlargement of the sella turcica, with tufting of the anterior and posterior clinoid processes. There is some invasion on the territory of the sphenoid sinuses posteriorly.

turbances. It is probably a chromophil adenoma, which reacted favorably to high voltage irradiation.

CASE 23.—*Pituitary tumor; probable chromophil adenoma (unverified). Atypical visual fields with nasal hemianopia on the right; marked headaches. Improvement following high voltage therapy.*

B. L., a woman, aged 40, a housewife, was referred by Dr. Leo J. Adelstein, Los Angeles, on Aug. 4, 1933. Approximately three years previously, general

acromegalic changes began to appear. There was enlargement of the hands and feet, together with changes in the features characteristic of the disease. They had continued to develop until examination. Approximately six months previously, it was discovered that she had diabetes mellitus. During the three weeks before examination she had several severe headaches. They were frontal and bitemporal and of short duration. Following her first severe headache she began to see double, and this persisted. She complained of weakness and tired easily. A year before, at the age of 39, amenorrhea occurred. There had been blurring of vision for the entire three weeks.

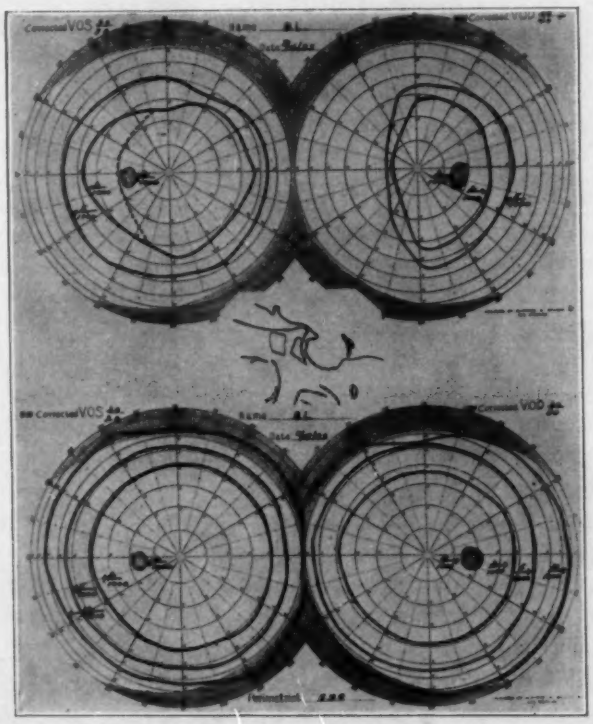

Fig. 23 (case 23).—Chromophil adenoma. Above, the fields show nasal hemianopia on the right and general contraction on the left before irradiation. The dotted line shows temporary constriction of the field occurring during a headache of short duration. Below, the fields show a return to normal following irradiation. The insert reveals the marked enlargement of the sella turcica, with nubbing of the anterior clinoid processes and partial erosion of the posterior clinoid processes. The sellar floor has obliterated the posterior portion of the sphenoid sinuses.

Examination revealed a woman 5 feet, 2 inches tall, weighing 127 pounds. She showed all the characteristics of marked acromegaly, in both her extremities and features. The lower jaw was prognathous, and her build suggested the masculine type. There was a complete palsy of the right abducens muscle. The eyegrounds showed overfilling of the veins, but the disks were not pale. The neurologic examination was unimportant. The Wassermann reaction of the blood was nega-

tive. Roentgenograms of the skull showed enlargement of the sella turcica, with almost complete erosion of the posterior clinoid processes. The floor of the sella turcica was irregular and had broken through into the sphenoid sinuses (fig. 23). The visual fields showed almost complete nasal hemianopia on the right and general contraction on the left. During the charting of the fields a severe headache developed, which lasted about two minutes. During this period a further contraction of the temporal field on the left could be charted, giving a vague left homonymous hemianopic appearance to the picture (fig. 23).

Comment.—The patient was given a course of high voltage therapy by Dr. J. Abowitz at the Cedars of Lebanon Hospital. Between August 8 and September 22 she received eleven doses of 300 r through the two temporal areas. The fields, on November 18 had practically returned to normal, the headache had decreased, and the palsy of the right abducens muscle had disappeared.

GENERAL COMMENT

Twenty-three cases of tumor of the pituitary gland have been presented, in each of which one or more courses of irradiation were given. Eight patients underwent operation, either before or following high voltage therapy. Two patients with adenocarcinoma (cases 4 and 5) showed no improvement, from the standpoint of expansion of the fields or of acuity, following irradiation. Their vision continued to fail, and both submitted to operation. One (case 4) died following the operation, apparently from cerebral edema. The second (case 5) had an exploratory operation by Dr. Learmonth at the Mayo Clinic. A malignant condition was suspected, and a small portion of the tumor was removed. It proved to be adenocarcinoma type II, according to the Mayo classification. Later, the patient was given high voltage and radium therapy without improvement in vision. In short, there was a general failure of vision covering a period of approximately two years.[20]

One patient with presumed cystic adenoma (case 9) showed no improvement following high voltage therapy. His vision continued to

20. Some have doubted if, in fact, a true adenocarcinoma of the pituitary gland exists. It is true that different tumors vary considerably in rate of growth, and that certain of them show marked rapidity of growth, as can be seen histologically. The rapidity of growth is judged largely by the frequency of mitotic cell division. If pituitary adenomas ever become truly malignant, they apparently differ from malignant changes in other ductless glands in that they do not metastasize outside the intracranial chamber. Confusion regarding this point has occasionally arisen in the epithelial type of carcinomas arising from the nasopharynx and metastasizing not only to the submaxillary glands, but elsewhere in the body. Such instances have been reported as malignant changes in craniopharyngeal pouch tissue. We are inclined to agree with Cushing that while the pituitary adenomas show different characteristics in rate of growth and certain cell changes, it is doubtful if they should ever be classed as truly malignant. We have followed the pathologist's classification in cases 4 and 5, listing the tumors as adenocarcinoma, although we doubt their actual malignancy.

fail in spite of a fairly long course of small doses. Operation was refused. The exact pathologic process has not been determined. A similar situation was present in case 21, in which exploration revealed a cystic chromophobe adenoma, as had been anticipated following failure to respond to irradiation. The fields promptly returned to normal following the operation.

Five patients with presumed chromophil tumor (1, 13, 18, 22 and 23), all of whom had acromegalic symptoms, showed marked improvement in the visual fields following irradiation. The patient in case 1 retained improved vision for more than nine years. One acromegalic woman (case 13) showed only slight constriction of the visual fields before irradiation, the fields returning to normal in about three months and remaining so for more than two years. Her headaches were not relieved, despite a liberal subtemporal decompression and irradiation. An attempt to explore the growth in case 18 was unsuccessful, owing to great intracranial pressure. A liberal decompression was therefore provided. The patient had the most intensive irradiation of any in the series, with remarkable improvement in vision. In fact, two years later his vision was practically normal. The improvement of vision could have been attributed only to high voltage therapy and not to operation on the growth. The decompression, however, made possible the employment of more intensive radiation than could otherwise have been used. He showed no untoward reaction following the treatments, and, in addition to recovery of practically normal vision was entirely relieved of headaches. A young woman (case 22) with early but definite acromegalic tendencies, responded very well to high voltage therapy. Her fields showed more rapid improvement than any other in the series. There was moderate constitutional reaction in connection with the treatments. In case 23, a woman with advanced acromegaly showed marked improvement of the fields following high voltage therapy. In addition, her headaches practically disappeared, and a palsy of the left abducens muscle disappeared. She had been under observation for four months. As nearly as can be judged, there was no advance in the acromegalic status of any of these patients. We feel that the acromegalic patient with a chromophil tumor reacts most favorably to deep irradiation.

Twelve patients with presumed chromophobe adenoma (cases 2, 3, 6, 7, 8, 10, 11, 14, 15, 16, 17 and 20) were given high voltage therapy. Their reaction was anything but uniform. In some instances slight improvement of vision was noted for a short time; in others an unlooked for improvement occurred and was maintained. Again, not only was there no improvement, but the vision continued to fail; the tumor in the latter cases was, with few exceptions, found to be cystic at subsequent operation.

One patient (case 6), whose tumor was classed as chromophobe adenoma, showed definite signs suggesting Fröhlich's syndrome. He was a lad of 16, in whom none of the secondary sexual characteristics had developed and who was 4 feet, 11 inches tall and weighed 95 pounds. Within two years following irradiation he gained 6 inches (15 cm.) in height and 16 pounds (7 Kg.) in weight, being 5 feet, 5 inches tall and weighing 111 pounds. In addition to this, his headaches disappeared entirely and the visual fields and acuity showed marked improvement. He has done well in school. A woman of 32 (case 7), with amenorrhea, showed marked improvement in acuity and definite enlargement of the visual fields, which was maintained for more than three years, but there was no return of menstrual function. The visual fields, consisting of a temporal hemianopia on the right and an island of vision in the upper nasal field on the left, remained practically stationary during this period. While irradiation did not improve the fields as much as could be desired, it apparently held them at a higher level than would otherwise have been the case. An exploratory operation on the gland may be necessary. Another woman (case 8) with a proved chromophobe adenoma, as shown by operation following irradiation, did not improve as much as one would wish. She was operated on approximately six weeks after the last course of irradiation. A fibrous type of chromophobe adenoma was found and partially removed. The wound healed by first intention, but after about ten days broke down in several places, which required several weeks to heal. The only patient (case 14) who came to autopsy following irradiation was a man of 68, with a chromophobe adenoma. He showed marked improvement in the fields and acuity following high voltage therapy. His death, some eighteen months later, was due to apoplexy. On histologic study, the pituitary gland showed a chromophobe adenoma, and the pathologist felt that it showed no increase in fibrosis or other cellular change as a result of the treatment. In short, no appreciable change as a result of irradiation was noted.

It had been the impression of one of us (C. W. R.) that fibrous changes in the tumors followed irradiation, making a subsequent surgical procedure less effective. However, one patient (case 21), with a proved chromophobe adenoma, came to operation within six days of very active high voltage therapy. This became necessary because of rapidly failing vision. A cystic chromophobe adenoma was encountered and partially removed. Because of the recent irradiation, it was expected that the tissues would react unfavorably at operation. This was not the case. There was no increase of bleeding, and the wound healed quickly by first intention.

COMMENT ON ROENTGEN THERAPY

The treatments were practically all given, except as otherwise noted, with constant factors of 186 kilovolts, a 0.75 mm. copper and a 1 mm.

aluminum filter, and a distance of 50 cm. from the skin to the target, through ports 2 inches (5 cm.) square. The factors used in the patients treated elsewhere were supposedly the same as ours. However, in some the actual amount and quality of radiation received are problematic.

In carrying out the treatments, multiple ports were used. It seemed practical to use two lateral, one anterior or frontal and one occipital, and if desired, one through the vertex, limiting their size with a lead apron or suitable cone. By rotating the treatments properly through the various areas, an opportunity for cross-firing and the delivery of considerable total radiation at the site of the tumor is possible. This can be accomplished without much danger to the hair or skin. We have had a few cases of transient epilation. These followed the earlier treatments, when proper rotation of the ports of entry was not observed. Epilation was seldom seen in the temporal areas, but more often in the frontal and occipital.

The distance from the skin to the pituitary gland through the different ports results, of course, in a varying dose being delivered to the tumor. The temporal areas, being nearest to the tumor, are the most efficient to use. Depending on the diameter of the individual patient's head, it is possible to deliver from 45 to 55 per cent of the dose at the skin to the tumor through each temporal port, from 35 to 45 per cent through the frontal and from 25 to 30 per cent through the occipital and vertex ports. The individual doses delivered to the tumor varied from 7 to 25 per cent of a skin erythema dose. The treatments were generally given on each alternate day, with 200 r on the skin as measured in air. If after a few treatments there was increased blurring of vision or if headaches resulted or increased in severity, the treatments were reduced to 150 r each, or a treatment or two was omitted. Occasionally, a patient was found who tolerated treatment exceptionally well and 150 or even 200 r could be given daily.

Two factors in connection with the treatment probably have a definite influence on the outcome: first, the sensitivity of the tumor to irradiation, and, second, the ability of the patient to take treatment in sufficient amount and rapidity to get effective dosage at the tumor. There seems to be no doubt that a previously performed decompression allows the delivery of more rapid and complete dosage to the pituitary gland without causing disagreeable after-effects. It is obvious that doses varying from 7 to 25 per cent, unless frequently and consistently given, will not deliver sufficient irradiation to have much influence on even the most sensitive tumor.

The patients in this series were practically all outpatients and under poor control. Some occasionally failed to keep their appointments, and the regularity of the dosage was therefore interrupted, so that the

depreciation effect was sometimes nearly as great as the subsequent dose; hence, accumulation might be practically at a standstill.

Owing to the rather alarming reaction shown by the first patient, to whom 200 and 300 r doses were given, treatment for subsequent patients was in the form of smaller doses given frequently and rapidly in an attempt to build up a saturation of satisfactory degree at the tumor. Either on account of the interval between treatments or the noncooperation of the patient, it may be impossible to build up a satisfactory dose at the tumor by this method. The results, perhaps, in this series would have been more satisfactory if it had been possible always to obtain a saturation dose. This could be accomplished only by having the patient under perfect control.

Irradiation, if at all intensive, probably causes a definite but varying degree of swelling and edema in the irradiated tissue. We believe that there may be an increase in the local pressure when this takes place inside an unopened skull. It might easily be shown in an accentuation of such symptoms as are due to increased pressure, especially headache, increased blurring of vision, nausea and vomiting.

SUMMARY AND IMPRESSIONS

An attempt has been made in a study of twenty-three cases to estimate the value of high voltage irradiation in the treatment of various types of tumors of the pituitary gland. The types analyzed have included: chromophil adenoma (five cases), chromophobe adenoma (thirteen cases), adenocarcinoma (two cases) and cystic chromophobe adenoma (three cases). The various types of tumors react differently. The problem as to the value of irradiation is far from solved, and at the present time a definite answer cannot be given.

Chromophil adenomas react most favorably to this form of treatment. The permanency of relief is indefinite. Cases have been cited in which visual improvement has been maintained from four months to nine years following high voltage therapy. One case, not included in the series, but one which came to the attention of one of us, showed improvement for ten years. While we have no case of basophilic adenoma to include in this group, reports which have begun to come in would seem to indicate that this type of tumor also reacts favorably to high voltage irradiation. Some believe that eosinophilic and basophilic cells are of a higher type than the indifferent chromophobe or chief cells. They should, theoretically, be more resistant to irradiation. On the contrary, they apparently react most favorably to this form of treatment.

Chromophobe adenomas have not responded uniformly to irradiation. This has been difficult to explain. It may be partly due to the fact that their treatment has not been uniform. In some cases the dosage

was insufficient and the course of irradiation incomplete. If the chromophobe cells, as some contend, are more embryonic than eosinophilic or basophilic cells, one would expect better results from irradiation. It must also be borne in mind that tumors of the pituitary gland do not necessarily run true to type, but may, to some degree, be mixed. The predominating cells may be of the chromophobe type, but there may also be present a smattering of other types of cells.

Adenocarcinoma of the pituitary gland apparently does not react favorably to high voltage irradiation. In view of the fact that mitosis of the cells is frequent one might expect that they would be more sensitive to irradiation. This does not appear to be true. There is a question whether, in fact, these tumors should be considered as true carcinomas; at all events, they do not metastasize extracranially.

Cystic adenomas of the chromophobe variety show no improvement following irradiation. This has been observed by others, and from the very nature of the growth is to be expected. Some of the tumors may be solid at first, later becoming cystic. It seems to us not unreasonable that, taken in conjunction with the clinical findings, a fairly accurate differential diagnosis between a cystic and a noncystic tumor can be made. This is judged largely by their reaction to high voltage irradiation. When apparent chromophobe tumors fail to react favorably to irradiation within a short time they are very likely cystic and more amenable to surgical treatment.

We are unprepared to state what, if any, morphologic changes in the gland can be demonstrated subsequent to high voltage irradiation. No demonstrable changes were seen in one case of chromophobe adenoma of this series which came to autopsy. However, the material was not obtained until a year after irradiation had ceased, and earlier demonstrable changes might easily have been missed.

Irradiation can be given more intensively if a decompression is first provided.

Apparently certain patients suffering from pituitary tumors gain from moderate to useful vision following irradiation. In some the gain may be held and the vision remain stationary for years. Without irradiation they would almost certainly become blind.

We have seen no definite regression in general acromegalic symptoms following irradiation. On the other hand, we have not seen any definite advance in symptoms. This point can be more definitely decided after a longer period of years has elapsed.

The literature contains many reports of brilliant results in changes in the fields immediately following partial surgical removal of tumors of the pituitary gland. Late results, however, are seldom given, so that it is more or less of a conjecture how long the improvement in vision may have lasted. In our experience, postoperatively, patients

without irradiation have maintained improved vision on an average of from one to three years. In various clinics, surgical intervention followed by high voltage irradiation is more or less a routine. It would not seem illogical in selected cases to employ irradiation first, in the hope that certain patients may be helped enough thereby to render surgical intervention unnecessary.

It should again be strongly emphasized that these cases should at all times be under the close scrutiny of a neurologic surgeon, who closely follows changes in the eyegrounds and fields, and who will frequently be called on to perform an operation. For at best, high voltage irradiation will give satisfactory results in only a certain percentage of cases. It does not replace surgical procedure, but rather acts as an adjunct to it.

EFFECT OF SUPRARENAL DENERVATION AND SPLANCHNIC SECTION ON THE SUGAR TOLERANCE OF DOGS

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In a previous study [1] we found that the removal of the celiac ganglion resulted in a decided, persistent rise of tolerance in every instance. The dogs became more sensitive to insulin. A denervation of the liver did not produce a rise in tolerance. To analyze the mechanism of our previous results, the rôle of the suprarenal glands was investigated in the study to be reported here.

Elsewhere [2] we summarized the literature on the effect of suprarenal denervation and of splanchnic section on sensitivity to insulin. It was reported uniformly that removal of the medulla, denervation of suprarenal glands or bilateral splanchnic section renders the animals more sensitive to insulin. The determination of hypersensitivity to insulin was only roughly quantitative, the criterion being whether convulsion occurred with a dose of insulin which prior to the operative procedure failed to cause convulsion. Regarding sugar tolerance before and after suprarenal denervation or splanchnic section, the only data available were found in a communication by Banting and Gairns,[3] who stated that twenty-four hours after double suprarenalectomy 2 Gm. of dextrose per kilogram given intravenously produced the same blood sugar curve as before operation. Finally, Ciminata [4] claimed, on the basis of a single experiment, that suprarenal denervation protects a pancreatectomized dog from diabetes. Critical collective reviews on

From the Department of Physiology and Pharmacology, Northwestern University Medical School.

1. de Takáts, G., and Cuthbert, F. P.: The Effect of Coeliac Ganglionectomy on the Sugar Tolerance of Dogs, Am. J. Physiol. **102**:615, 1932.

2. de Takáts, G., and Cuthbert, F. P.: Surgical Attempts at Increasing Sugar Tolerance, Arch. Surg. **26**:750 (May) 1933.

3. Banting, F. G., and Gairns, S.: Suprarenal Insufficiency, Am. J. Physiol. **77**:100, 1926.

4. Ciminata, A.: Einfluss der Durchschneidung der Nebennieren auf den Diabetes Mellitus, Klin. Wchnschr. **11**:150, 1932.

the physiology of the suprarenal glands were published by Bayer [5] and Britton.[6]

In this study our previously described methods of determining tolerance for sugar [7] and sensitivity to insulin [1] were applied to the study of the effect of bilateral suprarenal denervation. Bilateral section of the splanchnic nerves was scrutinized in the same manner.

METHODS OF EXPERIMENTATION

The tolerance to an intravenous injection of an isotonic dextrose solution at timed rates is a constant and repeatedly checked amount of dextrose that can be injected during an hour without producing glycosuria. It is never above 1.9 Gm. of dextrose per kilogram of body weight in the normal, well relaxed dog.[8] Following the operation repeated determinations of tolerance were made at monthly intervals. The dogs were observed for from six months to a year and a half and were finally killed to obtain histologic sections of the liver, suprarenal glands and pancreas. The sensitivity to insulin was determined by giving one-tenth unit per kilogram of body weight in 1 cc. of physiologic solution of sodium chloride. The blood sugar was determined before, and ten, twenty and thirty minutes and one hour and two hours after, the injection. Some observations were also made on the epinephrine hyperglycemia before and after operation, 0.02 mg. of epinephrine per kilogram of body weight being injected intravenously. Finally, the effect of double supradiaphragmatic vagotomy on the rise in tolerance obtained by splanchnic section was studied.

The technic of suprarenal denervation was as follows: An abdominal incision was made parallel to the right costal arch. The right suprarenal gland was exposed lateral to the vena cava. Between the diaphragm and the suprarenal gland, in the loose retroperitoneal tissue, the right major splanchnic nerve was picked up with a hook and dissected cephalad as far as possible, and a segment 1 inch (2.5 cm.) long was excised. The regeneration of this nerve takes place rapidly in the dog. A search was also made for the minor splanchnic filaments, which lie in a slightly deeper plane. Next, the large suprarenal plexus, which lies between the suprarenal and the celiac ganglion, was dissected out and severed; thus all of the nervous connections of the gland were interrupted. The same procedure was repeated on the left side, where, because of the absence of the liver and the vena cava, the dissection is much easier. In earlier experiments, a right suprarenalectomy was done, and the left suprarenal gland was denervated.

For bilateral splanchnic section, the right and left major and minor splanchnic nerves were excised, but the suprarenal plexus was not disturbed. The splanchnic nerves were also exposed in one dog above the diaphragm, in the posterior medias-

5. Bayer, G.: Handbuch der inneren Sekretion, Leipzig, Curt Kabitzsch, 1927, vol. 2, p. 641.

6. Britton, S. W.: Adrenal Insufficiency and Related Considerations, Physiol. Rev. **10**:617, 1930.

7. de Takáts, G.; Hannett, F.; Henderson, D., and Seitz, I. J.: The Effect of Isolating the Tail of the Pancreas on Carbohydrate Metabolism, Correlation of Internal and External Pancreatic Secretion; Arch. Surg. **20**:866 (May) 1930.

8. Determinations of tolerance carried out by several workers in this laboratory in over fifty normal dogs yielded an average of 1.87 Gm. of dextrose per kilogram of body weight per hour.

tinum, but this approach offered no advantages in the dog. Double supradiaphragmatic vagotomy was performed through an incision in the eighth or ninth intercostal space. The pleural cavity was rapidly opened, the esophagus was picked up and the two vagus nerves were cut to the right and to the left of the esophagus. The resulting pneumothorax was quickly expressed, and the pleural gap was sutured rapidly in maximal expiration, with two heavy sutures approximating the two neighboring ribs. The intrapleural part of the operation usually did not take more than a minute or two. The intestinal muscles and skin were carefully sutured.

TABLE 1.—*Rise in Sugar Tolerance Following Suprarenal Denervation*

Dog	Preoperative Tolerance,* Gm. per Kg. per Hour	Postoperative Tolerance,† Gm. per Kg. per Hour	Rise, per Cent
69	1.8	3.35	80.6
70	1.84	2.92	58.6
79	1.8	2.85	58.3
82	1.8	2.94	63.3
83	1.87*	2.92	62.22
84	1.87*	2.82	56.66
89	1.87*	2.96	64.44
90	1.8	2.78	54.44
91	1.8	3.00	66.66
93	1.87*	3.00	66.66
95	1.87*	2.91	61.66
96	1.87*	2.57	42.77
Average	1.84	2.94	61.36

* Determinations of tolerance on over fifty normal dogs gave figures of 1.87 Gm. of dextrose per kilogram per hour. In these dogs the preoperative tolerance was not determined.
† Average of several determinations.

TABLE 2.—*Sensitivity to Insulin Following Suprarenal Denervation*

Dog	Post-operative Period, Weeks	Blood Sugar, Mg. per 100 Cc.					
		During Fasting	Minutes After Injection of Insulin				
			10	20	30	60	120
70	10	74.2	55.2	37.4	39.0	46.7	68.7
79	12	88.5	69.5	31.4	31.2	31.2	62.5
82	11	99.0	86.2	55.6	45.1	51.3	99.0
83	8	84.7	68.0	42.7	40.2	49.5	74.6
84	9	75.8	52.3	34.9	41.3	43.7	76.9
89	3	73.0	62.9	52.3	45.7	46.3	70.4
Average		82.5	65.7	42.4	39.6	44.8	75.3

RESULTS

The rise in sugar tolerance following suprarenal denervation is shown in table 1. The average rise in twelve experiments was 61.36 per cent of the preoperative level, and the rise varied from the maximum of 3.35 Gm. of dextrose per kilogram per hour to the minimum of 2.57 Gm. per kilogram per hour. As in the previous series of dogs subjected to celiac ganglionectomy, the maximal rise in tolerance was obtained after the animal had recovered from the operation and was maintained indefinitely unless an infection or intestinal complication developed. Intestinal complications will be discussed later.

The response of these dogs to insulin was definitely increased. The blood sugar curves are shown in table 2. Determinations were made between three weeks and eleven weeks after operation. A composite graph (chart 1) comparing the susceptibility to insulin of normal dogs with that of dogs which underwent celiac ganglionectomy, suprarenal denervation, splanchnic section and splanchnic section with added bilat-

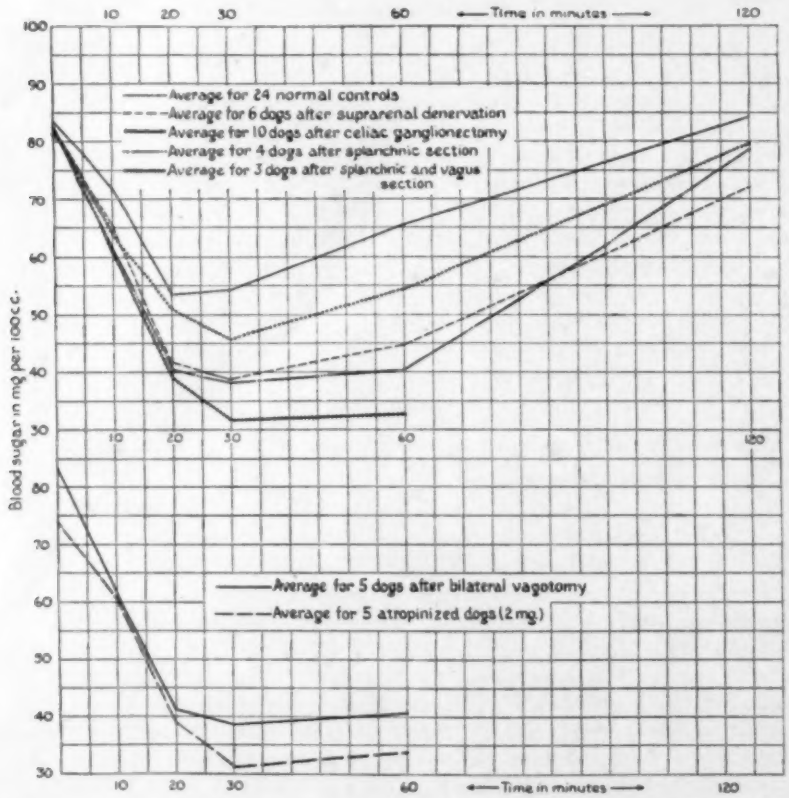
Time in minutes
Blood sugar in mg. per 100 c.c.
Average for 24 normal controls
Average for 6 dogs after suprarenal denervation
Average for 10 dogs after celiac ganglionectomy
Average for 4 dogs after splanchnic section
Average for 3 dogs after splanchnic and vagus section
Average for 5 dogs after bilateral vagotomy
Average for 5 atropinized dogs (2 mg.)

Chart 1.—Curves showing the sensitivity to insulin, as indicated by the blood sugar. One-tenth unit of insulin was given intravenously in 1 cc. of physiologic solution of sodium chloride. The blood sugar was determined by the modified Folin-Wu method, before the administration of insulin and ten, twenty, thirty, sixty and one hundred and twenty minutes afterward. Note that celiac ganglionectomy, suprarenal denervation and splanchnic section produce an increase in the sensitivity to insulin. The average of twenty-four curves for normal controls is low, because some of the determinations were made during excessive heat in the summer, and high temperatures increase the response to insulin (Krogh's, Trevan's and our observations). Following the operative procedures, the effect of heat is not noticeable on the sensitivity to insulin. Note also that bilateral vagotomy or atropinization does not diminish or abolish the reaction to insulin, as claimed by Babkin; on the contrary, it increases the sensitivity.

eral vagotomy reveals that the four groups of operations resulted in a definite enhancement of the action of insulin on blood sugar curves.

The rise in sugar tolerance following bilateral splanchnic section closely parallels that seen after suprarenal denervation (table 3). The sensitivity to insulin has also increased (table 4). The average figures check closely with those seen in table 2.

The responses to epinephrine of dogs in which suprarenal denervation was done was identical to that of dogs in which splanchnic section was done, so that the results for both experiments are shown in one table (table 5). A comparison with the figures obtained for dogs pre-

TABLE 3.—*Rise in Sugar Tolerance Following Bilateral Splanchnic Section*

Dog	Preoperative Tolerance, Gm. per Kg. per Hour	Postoperative Tolerance, Gm. per Kg. per Hour	Rise, per Cent
64	1.9	2.81	47.8
100	1.8	2.90	61.1
102	1.8	2.89	60.5
103	1.8	2.79	55.5
105	1.8	2.73	51.8
106	1.8	2.88	66.6
97	1.8	3.45	91.6
98	1.8	2.74	52.2
104	1.8	2.61	45.0
Average	1.8	2.86	58.8

TABLE 4.—*Sensitivity to Insulin* After Bilateral Splanchnic Section*

During Fasting	Minutes After Injection of Insulin				
	10	20	30	60	120
86.2	55.3	49.6	51.8	52.2	85.5
69.5	41.0	27.2	25.1	33.1	....
88.5	69.5	31.4	31.2	28.3	62.5
90.0	86.2	55.6	45.1	51.3	90.0
85.8	65.0	40.95	38.3	41.2	82.3

* The figures represent milligrams of sugar per hundred cubic centimeters of blood.

vious to operation (table 6) indicates that these operations definitely depress, although they do not entirely suppress, hyperglycemia due to epinephrine. In chart 2 the upper two curves illustrate the effect of splanchnic section on epinephrine hyperglycemia, the dose of 0.02 mg. of epinephrine per kilogram of body weight having been given. The middle two curves show the effect of suprarenal denervation on the response to epinephrine which is equally definite, but the smaller dose of 0.01 mg. per kilogram was given intravenously. The lower curves represent the average for seven normal animals and eight animals on which operation had been performed. The dose was 0.02 mg. per kilogram of body weight. The blood sugar during fasting is

lower and the peak of the rise, which appears between five and ten minutes after the injection, is lower in the group with suprarenal denervation.

When supradiaphragmatic double vagotomy was added to bilateral splanchnic section, the tolerance did not change except in one instance,

TABLE 5.—*Response of the Blood Sugar* to Epinephrine in Dogs with Suprarenal Denervation or Splanchnic Section*

During Fasting	Minutes After Administration of Epinephrine				
	10	20	30	60	120
95.2	104.8	96.6	95.2	89.7	84.4
66.0	58.7	57.3	55.6	59.3	71.2
83.3	101.0	97.6	75.2	76.1	81.6
71.3	84.4	79.7	70.8	74.7	71.7
83.0	94.3	81.6	81.3	74.9	70.0
80.3	94.0	81.3	75.6	78.3	79.1
72.7	80.6	80.8	64.4	69.3	71.8
81.9	94.3	93.0	90.1	88.1	84.0
79.2	89.0	83.5	76.0	76.3	76.9

* The figures represent milligrams of sugar per hundred cubic centimeters of blood.

TABLE 6.—*Hyperglycemia* Due to Epinephrine in the Normal Dog*

During Fasting	Minutes After Administration of Epinephrine				
	10	20	30	60	120
100.5	122.7	117.6	107.0	98.6	85.9
105.3	154.7	160.6	137.2	127.1	99.4
108.7	122.0	137.0	122.7	119.0	111.7
102.1	87.8	93.9	97.6	88.9	88.5
85.1	119.0	92.7	90.5	....	87.4
86.6	114.3	99.0	87.4	86.2	....
102.1	110.5	98.6	97.1	100.5	103.4
98.6	118.7	114.2	105.6	103.4	96.05

* The figures represent milligrams of sugar per hundred cubic centimeters of blood.

TABLE 7.—*The Effect of Double Vagotomy on the Rise in Sugar Tolerance Obtained After Bilateral Splanchnic Section*

Dog	Sugar Tolerance*	
	Before Vagotomy	After Vagotomy
102	2.73	2.73
97	3.45	3.19
98	2.74	2.61

* Expressed in grams per kilogram per hour.

but here the determination was done too soon after the operation (table 7). Nor did vagotomy change the increased sensitivity to insulin obtained after splanchnic section; if anything, it slightly increased it. Doses of atropine of from 2 to 2.5 mg. given before the administration of 5 units of insulin intravenously did not diminish the action of the insulin and the blood sugar values showed a close similarity to those obtained after double vagotomy (chart 1, lower two curves).

OTHER OBSERVATIONS

The surgical mortality was very low, but some animals were so listless and adynamic after the suprarenal denervation that they were given ephedrine in doses of 15 mg. twice a day for the first day or two after

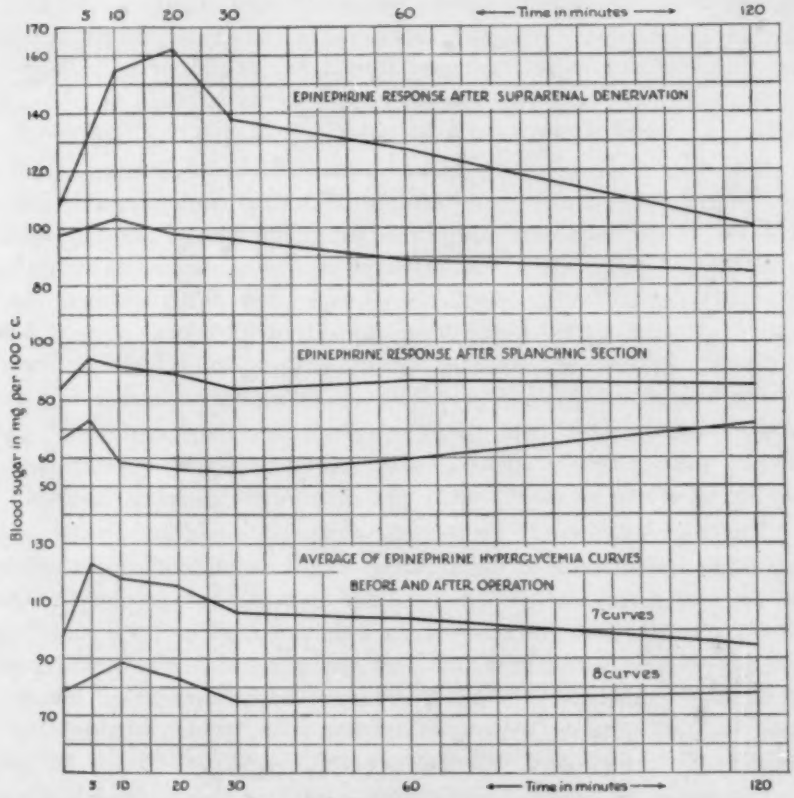

Chart 2.—Curves showing hyperglycemia due to epinephrine. Epinephrine was given intravenously in doses of 0.02 mg. in 1 cc. of physiologic solution of sodium chloride. Tests for blood sugar were made before the injection and five, ten, twenty, thirty, sixty and one hundred and twenty minutes afterward. The upper and middle pairs of curves, showing the response following suprarenal denervation and splanchnic section, respectively, represent single experiments before and after operation, while the lowest two curves represent averages after both types of operation. In the three groups the upper curve is preoperative, and the lower curve postoperative. Note that the blood sugar during fasting is lower after suprarenal denervation or splanchnic section. The rise of the blood sugar curve is less pronounced after these two operations, or may even be inverted in individual curves (not shown in this graph). The curves indicate that glycogen is more difficult to mobilize after the operation, provided the glycogen content of the liver is not diminished. Our unpublished data indicate that there is a rise of glycogen in the liver after splanchnic section.

the operation. About one third of the animals had postoperative diarrhea, but this was readily controlled by atropine.

All of the dogs studied in the series were killed, and autopsies were performed at the conclusion of the experiment. The cut ends of the splanchnic nerves were found matted together in a neuroma in most of the earlier cases. We have since removed larger segments and believe that a regeneration of the splanchnic nerve can hardly be prevented, unless the proximal stump is implanted into a peripheral nerve.[9] Sections of the liver, pancreas and suprarenal glands were taken as a routine, and only a brief summary of the observations will be presented here.

The liver macroscopically looked normal. The surface was smooth, and the color and consistency were normal. On histologic section, however, the liver cells seemed large; the protoplasm was light and slightly granular and the nucleus was often pushed to one side. This change was particularly obvious around the central vein. Whether these observations mean an abnormally high deposit of glycogen is now being studied.[10] Preliminary staining for fat with sudan III did not reveal an unusual amount of lipoid substance. There was no increase in connective tissue. The small bile ducts and the portal and the hepatic venules were generally dilated. The entire liver was hyperemic. In dog 94, all of the smallest vessels were dilated and filled with blood.

The pancreas seemed to be more firm than is normal and was granular in consistency in some of the animals. Its color and size were normal. On section, there was an unmistakable increase in vascularity. Not only the vessels but the ducts were wide open. The acini and small ducts were filled with secretion. The size and number of islands were not studied numerically in serial sections; in certain slides, however, there was an unusual hyperemia of the islets, which enabled us to visualize the complicated vascular network.

The denervated suprarenal glands seemed of normal size and consistency, although in two of the fifteen animals studied the glands were small and atrophic. The medullary veins were gaping, and the chromaffin substance stained well. The cortex was loaded with lipoid substance and showed mitotic activity between the zona glomerulosa and the zona fasciculata. The cortical veins were not so dilated as the medullary ones. The general impression was that of increased fat storage in the cortex, the medulla being unchanged except for the venous hyperemia.[11]

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9. Dr. S. W. Ransom made this suggestion.

10. von Gierke, E.: Hepato-Nephromegalia glycogenica, Beitr. z. path. Anat. u. z. allg. Path. **82**:497, 1929.

11. Dr. R. A. Jaffé, pathologist of the University of Illinois and of the Cook County Hospital, looked over these slides.

COMMENT

When the rise in intravenous sugar tolerance following suprarenal denervation and splanchnic section and our previously reported results following celiac ganglionectomy are compared, it will be seen that they are practically identical. Certain breeds of dogs, such as airdales, respond with higher rises in tolerance than others, but an average rise to from 2.8 to 2.9 Gm. of dextrose per kilogram per hour was obtained in all three groups of experiments. The susceptibility to insulin is also markedly exaggerated. We are aware of the many factors that influence the response to insulin, such as seasonal and atmospheric variations, previous nutrition, dehydration and temperature; nevertheless, the severance of the sympathetic innervation to the triad of liver, pancreas and suprarenal glands makes the animal unmistakably sensitive to insulin. The curves showing the response to epinephrine, on the other hand, indicate that sugar is mobilized with more difficulty from the liver, assuming, of course, that there is enough glycogen available for mobilization.

The influence of double vagotomy on the rise in sugar tolerance following suprarenal denervation or splanchnic section was found to be negligible. Quigley and his co-workers have found [12] that secretion of insulin following hyperglycemia is at least as active with both vagus nerves cut as in the normal animal. The rises in tolerance which we noted, therefore, do not seem to be explained on the basis of a vagosympathetic imbalance. While we have previously reported that denervation of the liver alone did not seem to produce a rise in tolerance or an increased sensitivity to insulin, there are uniform histologic changes in the liver and the portal system that require further study. The liver cell is loaded with a substance, and if this proves to be glycogen, the changed responses to insulin and epinephrine might be explained by a "glykopexy," or increased glycogen fixation.

The effect of splanchnic section on the suprarenal medulla has been studied by a large number of workers.[5] Important is the work of Hoshi,[13] who observed disappearance of nerve fibrils in the medulla within from four to eight days after splanchnic section. Section of the vagus has no effect on the microscopic picture. Hoshi stated the belief that there are no ganglions in the medulla and no synapsis in the celiac ganglion, which would mean that both splanchnic section and celiac ganglionectomy would be postganglionic neurotomies.

12. Quigley, J. P.; Halloran, W. R., and Barnes, B. O.: Variations in Blood Sugar Values of Normal and Vagotomized Dogs Following Glucose Administration, J. Nutrition **5**:77, 1932.

13. Hoshi, T.: Morphologisch-experimentelle Untersuchungen über die Innervation der Nebennieren, Mitt. d. allg. Path. u. path. Anat. **3**:328, 1927.

That hypoglycemia due to insulin stimulates medullasuprarenal secretion has been sufficiently emphasized by Cannon.[14] Kahn [15] showed that histologic changes occur in the medulla of the suprarenal glands and also in the aortic paraganglion following the administration of insulin, but that this can be effectively prevented by splanchnic section.

Raab [16] expressed the belief that epinephrine is the direct antagonist of insulin so far as glycogen fixation in the liver is concerned. If one inhibits the secretion of epinephrine that follows the administration of insulin by splanchnic section, an increased glycogen fixation should result.

The work of Kutschera-Aichbergen [17] deserves to be mentioned in connection with our work. He believed that he had shown that, while epinephrine usually flows through the central vein to the vena cava, the vein, which is unusually muscular, may be closed by spasm; the result is the shunting of the epinephrine through the cortical veins and into the portal system, whence it acts more directly on the glycogen. Kutschera-Aichbergen explained piqûre glycosuria by such a spasm of the central vein. Splanchnic section may abolish such central impulses to the central vein, and it has been repeatedly shown that no central hyperglycemia can be produced after section of the splanchnic nerve (Mock and de Takáts [18]).

The rôle of the suprarenal cortex in carbohydrate metabolism has been recently discussed by Britton and Silvette [19] and Silvette.[20] According to these investigators, corticosuprarenal extract increases the rate of glycolysis in vitro, raises the liver glycogen and increases the blood sugar in the animal suffering from cortical insufficiency. The observations of Tokomitsu [21] are interesting; he stated that following ligation of the pancreatic duct in the rabbit, the suprarenal cortex enlarges from one and one-half to two times its original size and many mitoses are seen at

14. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: A Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, Am. J. Physiol. **69**: 46, 1924.

15. Kahn, R. H.: Ueber die zentrale Reizung der Nebennieren und der Paraganglion während der Insulinvergiftung, Arch. f. d. ges. Physiol. **212**:54, 1926.

16. Raab, W.: Glykogen-Fixation mit Insulin, Klin. Wchnschr. **3**:1678 (Sept. 9) 1924.

17. Kutschera-Aichbergen, H.: Nebennieren Studien, Frankfurt. Ztschr. f. Path. **28**:262, 1922.

18. Mock, H., and de Takáts, G.: Hyperglycemia Following Head Injuries, Ann. Surg. **90**:190, 1929.

19. Britton, S. W., and Silvette, H.: The Apparent Prepotent Function of the Adrenal Glands, Am. J. Physiol. **100**:701, 1931.

20. Silvette, H.: Effects of Cortico-Adrenal Extract on Glycolysis in Vitro, Am. J. Physiol. **102**:693, 1932.

21. Tokomitsu, Y.: Ueber eine neue Funktion der Nebennierenrinde, Mitt. u. allg. Path. u. path. Anat. **1**:161, 1921.

the zona spongiosa. He thought that the cortex and the pancreatic islets are synergists, and that a compensatory cortical hypertrophy prevents the animals from becoming diabetic. When the cortex was removed, glycosuria of long duration developed. The report of a case of diabetes in which the patient, who died in coma, was resistant to insulin, was published by Chiari;[22] a marked hypertrophy of the cortical cells was found in a true cortical adenoma. In a previous communication[2] we reported cortical enlargement following ligation of the tail of the pancreas.

What suprarenal denervation or splanchnic section does to cortical secretion, particularly in regard to carbohydrate metabolism has not been studied so far. Our histologic observations indicate that there is an increased storage of fat. Cortical atrophy is known to occur after hypophysectomy. Cortical hypertrophy can be induced by the adrenotropic hormone of the anterior pituitary gland, and this may be one of the links between carbohydrate metabolism and the pituitary gland.

SUMMARY

Suprarenal denervation and section of the splanchnic nerve are equally effective in raising the sugar tolerance of normal dogs. Thus the previously reported effect of celiac ganglionectomy can be explained by its denervating effect on the suprarenal glands. The dogs are more responsive to insulin and less responsive to the hyperglycemic action of epinephrine. Bilateral vagotomy does not diminish the rise in sugar tolerance obtained by these operations. These data add to the knowledge of the stimulating effect of the sympathicosuprarenal system on the mobilization of glycogen. The interruption of this mechanism may lead to increased glycogen storage or fixation of glycogen in the liver.

NOTE.—Since this article went to press, it has been definitely established that splanchnic section produces an increased storage and also an increased fixation of glycogen.

22. Chiari, H.: Ein Fall von Diabetes mit Hypertrophie der Nebennieren-Rinde, Wien. klin. Wchnschr. **42**:1318, 1929.

GASTRIC SECRETION

V. ACHLORHYDRIA FOLLOWING PARTIAL GASTRECTOMY FOR ULCER: STUDIES WITH HISTAMINE AND THE TRANSPLANTED GASTRIC POUCH

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The operation of partial gastrectomy has furnished an opportunity for the study of many of the problems of gastric physiology. The present paper is not primarily concerned with the results following this procedure. These have recently been discussed by Berg,[1] who introduced the operation in this country as the procedure of choice in the treatment of gastric and duodenal ulcer. But in spite of the numerous advances in physiology and their evident bearing on the subject, there still exists an apparent misunderstanding of the mechanisms involved. Since considerations of function are at least as important as those of structure, it may not be amiss to emphasize again the underlying facts and at the same time add some clarifying experiments.

The first point to grasp is that the gastric secretion following a meal is not a single response to one type of stimulus. It is the total of responses to at least three, and probably more, entirely separate groups of stimuli. Further, the mechanisms of these groups vary considerably. It is possible to influence one without affecting the others.

Briefly considered, the three chief phases are (1) primary (psychic, cephalic); (2) secondary (gastric, chemical), and (3) intestinal.

(1) The primary phase is reflex, and the reflex pathway reaches the stomach over the vagus system. Seeing or smelling food may initiate the stimulus and tasting, chewing and swallowing continue it. The secretion starts about five minutes after the beginning of the sensory stimulation and persists for about two hours after it ceases. The secretion varies in amount, being more profuse during hunger than after the appetite is appeased. Section of the vagi suppresses this secretion.[2]

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† Dr. Klein died on Oct. 2, 1932.

From the Service of Dr. A. A. Berg and the Department of Laboratories, Mount Sinai Hospital.

1. Berg, A. A.: The Radical Operative Cure of Gastric and Duodenal Ulcer, S. Clin. North America **8**:1167, 1928; The Mortality and Late Results of Subtotal Gastrectomy for the Radical Cure of Gastric and Duodenal Ulcer, Ann. Surg. **91**:340, 1930.

2. (*a*) Uschakow: Dissert, St. Petersburg, p. 20; quoted by Babkin, B. P.: Die äussere Sekretion der Verdauungsdrüsen, Berlin, Julius Springer, 1928, p. 398. (*b*) Pavlov, I. P.: The Work of the Digestive Glands, ed. 2, London, C. Griffin & Company, 1910.

(2) The secondary or chemical phase begins after the entrance of food into the stomach. It is due to chemical substances in the food. These do not directly stimulate the secretory cells. There are no acid cells in the antrum or distal portion of the stomach. They are all situated in the body and fundus. But it is through the antrum that the chemical stimuli act.[3] This fact is physiologically well established, but clinically is not so well known. The mechanism is only partly understood. The chemicals from the food (secretogogues) either are directly absorbed into the blood stream or produce a hormone in the antrum which is absorbed and carried to the secretory cells through the blood. It is the antrum or the site of the chemical stimulation that is removed by the operation of partial gastrectomy.

(3) The intestinal stimulus is not so well understood as the others. It apparently starts late after a meal (from one to six hours) and accounts for only a small part of the secretion.[4]

In addition to those clearly defined phases, there is the spontaneous secretion. This seems to be due chiefly to conditioned reflexes reaching the stomach over the vagi.[5] But there may also be chemical stimuli acting through the blood.[6]

Following partial gastrectomy, which removes the antrum of the stomach, achlorhydria is produced in a certain proportion of cases. In table 1 are shown the results reported in a previous paper.[7] The observations on a much larger group are now in preparation.

To study experimentally in the dog the effects of the elimination of the second or chemical phase, a transplanted subcutaneous pouch was used.[3a] Intra-abdominal section of the vagi, no matter how carefully performed, frequently misses some branches, especially those that may be given off just above the diaphragm. With the transplanted pouch these objections did not hold.

All connection with the vagus and splanchnic nerves and the gastric vessels was eliminated. The pouch was dependent on the abdominal wall for its blood supply. The primary, or reflex, and the intestinal phase could still act by transmitting stimuli through the blood. The response

3. (*a*) Klein, E., and Arnheim, E.: Gastric Secretion: I. A Transplanted Subcutaneous Gastric Pouch, Arch. Surg. **25**:433 (Sept.) 1932. (*b*) Ivy, A. C.: The Rôle of Hormones in Digestion, Physiol. Rev. **10**:282, 1930. (*c*) Babkin, B. P.: Die äussere Sekretion der Verdauungsdrüsen, Berlin, Julius Springer, 1928, p. 398.

4. Ivy, A. C.; Lim, R. K. S., and McCarthy, J. B.: The Intestinal Phase of Gastric Secretion, Quart. J. Exper. Physiol. **15**:55, 1925.

5. Babkin,[3c] p. 190.

6. Klein, E.: Gastric Secretion: IV. Effect of Atropine on the Secretion of Transplanted Subcutaneous Gastric Pouches, Arch. Surg. **26**:246 (Feb.) 1933.

7. Klein, E.: Gastric Secretion After Partial Gastrectomy, J. A. M. A. **89**: 1235 (Oct. 8) 1927.

to test meals of meat and water was studied (table 2). A partial gastrectomy was then performed to remove the secondary phase. After this, no free acid was secreted in the pouch during the first six hours after a meal (table 2). However, a small dose of histamine produced a

TABLE 1.—*Effect of Partial Gastrectomy on the Acidity of the Gastric Contents*

Type of Ulcer	Anacid, per Cent	0 to 20, per Cent of Patients	20 to 50, per Cent of Patients	50 and Above, per Cent of Patients	Number of Patients
Duodenal					
Before operation	..	4	36	60	50
Recent*	9	9	46	36	11
Old	25	41	17	17	12
Gastric					
Before operation	..	28	60	12	25
Recent	45	33	11	11	9
Old	100	..	..	..	3
Gastrojejunal					
Before operation†	..	11	67	22	9
Recent	25	25	50	..	4
Old	50	..	50	..	2

* "Recent" refers to patients examined immediately after operation and "old," to patients examined six months after operation.

† "Before operation" refers to patients examined before partial gastrectomy.

TABLE 2.—*Effect of Partial Gastrectomy on the Secretion of a Transplanted Subcutaneous Gastric Pouch Deprived of Vagus and Sympathetic Nerve Supply*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Acid
Before partial gastrectomy			
1	0.2	0	0
Fed 250 Gm. of meat			
2	0.6	16	33
3	1.1	27	54
4	0.7	14	43
5	0.8	25	50
6	0.6	20	45
After partial gastrectomy			
1	0.2	0	0
Fed 250 Gm. of meat			
2	0.5	0	0
3	0.2	0	0
4	0.2	0	0
5	0.6	0	0
6	0.4	0	0
7	0.2	0	0

normal response (table 3), showing that the glandular cells could respond promptly to a chemical stimulus.

When, therefore, the primary vagal phase was absent, the removal of the secondary or gastric phase by partial gastrectomy resulted in anacidity in the pouch during the period when the secretions from these two stimuli are normally present. Of course, intestinal neutralization could play no part in the anacidity occurring in the pouch.

Previous evidence showing the relation of antrectomy to the phases of gastric secretion is that of Gross [8] and Sawitsch and Zeliony,[9] who showed that chemical stimuli producing the secondary phase act not on the body and fundus but on the antrum.[8] Smidt [10] studied the secretion in dogs with Pavlov pouches, and then did a partial gastrectomy. The secretory curves were lowered in such a way as to show suppression of the secondary phase.

One may say with fair certainty, then, that partial gastrectomy removes the secondary or chemical phase of gastric secretion if it is sufficiently extensive to remove the entire antrum. Pylorectomy, which

TABLE 3.—*Effect of Histamine on the Secretion of a Transplanted Subcutaneous Gastric Pouch Before and After Partial Gastrectomy*

Hour	Volume of Juice, Cc.	Free Hydrochloric Acid	Total Acid
Before partial gastrectomy			
1	0.5	0	0
2	0.6	0	0
0.2 mg. of histamine subcutaneously			
3	2.6	32	56
4	1.2	18	48
5	1.0	0	28
6	1.0	0	10
7	0.5	0	0
After partial gastrectomy			
1	0.3	0	0
2	0.4	0	0
0.2 mg. of histamine subcutaneously			
3	2.3	12	32
4	1.1	12	48
5	1.1	0	15
6	0.8	0	8
7	0.6	0	6

is so often confused with partial gastrectomy, is not the same operation. Part of the antrum is left. Also, if the pylorus is left, some of the antrum remains.

Table 1 shows, nevertheless, a wide variation in the acid secretion following partial gastrectomy in man. The results range from anacidity (most common in cases of gastric ulcer) to hyperacidity (most common in cases of duodenal ulcer). Can any cause be assigned for these variations? Since the secondary phase has been eliminated, and since the intestinal phase starts late and apparently does not produce a high rate

8. Gross, W.: Beitrag zur Kenntnis der Sekretionsbedingungen des Magens nach Versuchen am Hund, Arch. f. Verdauungskr. **12**:507, 1906.

9. Sawitsch, W., and Zeliony, G.: Zur Physiologie des Pylorus, Arch. f. d. ges. Physiol. **150**:128, 1913.

10. Smidt, H.: Experimentelle Studien am nach Pavlov isolierten kleinen Magen über die sekretorische Arbeit der Magendrüsen nach den Resektionen Billroth I und II, sowie nach der Pylorusausschaltung nach v. Eiselsberg, Arch. f. klin. Chir. **125**:26, 1923.

of secretion, the acidity in the three hour Rehfuss tests, when it persisted after gastrectomy, would seem most likely to be due to the primary phase or to spontaneous secretion. Of course, nothing has been done to remove these.[11]

The amount of acid present in the test meal after the operation is, therefore, caused by the following factors:

1. The amount of secretory stimulation that persists. This is probably chiefly vagal and reflex. No doubt it is greater in some persons than in others. The possibilities of intestinal stimulation and of parenteric stimulation must also be borne in mind.

2. The relative percentage of the secretion which before operation is due to the secondary phase. For argument's sake, assume that in one case it is 30 per cent and in another 60 per cent. In the latter, partial gastrectomy would reduce the postoperative acidity much more than in the former. It is likely that the second condition is more frequent after the operation for gastric ulcer than after duodenal ulcer.

3. The amount of neutralizing substances. Pancreatic juice, bile, saliva and the test meal itself neutralize acid. That these are not, however, the sole factors in the production of anacidity, as Portis and Portis [12] contended, is clear from what has been stated previously.

4. A change in the secreting cells themselves. It is possible that in some cases such a change may occur. This will be discussed more fully later.

Briefly, then, the considerations thus far advanced show that anacidity results when the removal of the gastric secondary phase reduces the secretion sufficiently to permit neutralization of the remaining secretion by food and intestinal regurgitation. When a large proportion of the secretion is secondary, when the primary, or vagal, phase is not profuse and when a great amount of regurgitation is present, anacidity results; when the conditions are reversed, acidity will persist. Of course, these are the extremes, and all degrees of variations intervene.

Table 1 shows that in cases of gastric ulcer the tendency toward achlorhydria after operation is greater than in those of duodenal ulcer. Although the evidence is not conclusive, it seems highly probable that the former conditions are more often approximated in cases of gastric ulcer and the latter in those of duodenal ulcer.

A further contributing element is that in the case of duodenal ulcer the first part of the duodenum is also removed during the operation. Since inhibitory impulses to gastric secretion originate in this part

11. The possibility that some of the secretion of acid which persists is due to stimuli of parenteric origin also cannot be excluded.

12. Portis, S. A., and Portis, B.: Effects of Subtotal Gastrectomy on Gastric Secretion, J. A. M. A. **86**:836 (March 20) 1926.

(Sokolov,[13] Smidt,[10] Lim, Ivy and McCarthy [14]), the removal of these inhibitions tends to permit greater secretion after operation in cases of duodenal than in those of gastric ulcer.[15]

For these reasons, as stated in a previous paper,[16] section of the left, or anterior, vagus has been added to the operation of partial gastrectomy when the preoperative acidity is very high. The additional reduction of part of the primary vagal phase is usually sufficient to produce achlorhydria.

There is, however, one further element that enters into the production of anacidity after operation for both duodenal and gastric ulcer. This is shown by studies with histamine. When using histamine as a gastric stimulant, one should recognize clearly that the resultant stimulation is not exactly comparable to that of the test meal. First, histamine is a powerful chemical stimulus acting directly on the cells and stimulating chiefly the secretion of hydrochloric acid; [17] second, the primary or vagal phase does not enter into the resultant secretion, and, third, the juice secreted into the stomach is obtained in a purer state, since no food from a test meal is mixed with it. These facts should be remembered when comparisons are made with the various secretory tests in man.

After partial gastrectomy histamine tests were performed on seventeen persons who showed an anacidity to the Rehfuss test meal with gruel. All of the patients had free acid before operation. Five-tenths milligram of histamine hydrochloride was injected subcutaneously, and the gastric secretion was extracted every fifteen minutes for three hours. All but four of the patients showed acid after injection of the histamine. The degree varied from a small amount in only one tube to the presence of free acidity throughout the three hours of the test.

In these cases it is evident that acid could still be secreted. However, the amount had been so reduced by the operation that with the ordinary stimulus of the test meal the resultant acid secretion could be neutralized by food and intestinal regurgitation. It should be emphasized that the results which follow stimulation by food are probably more in line with

13. Sokolov, quoted by Pavlov.[2b]

14. Lim, R. K. S.; Ivy, A. C., and McCarthy, J. B.: Contributions to Physiology of Gastric Secretion by Local and Chemical Stimulation, Quart. J. Exper. Physiol. **15**:13, 1925.

15. Experiments are now under way to determine whether some part of the preoperative hyperacidity so common in cases of duodenal ulcer is due to interference with inhibition from the duodenum.

16. Klein, E.: Left Vagus Section and Partial Gastrectomy for Duodenal Ulcer with Hyperacidity, Ann. Surg. **90**:165 (July) 1929.

17. Babkin, B. P.: The Value of Histamine as a Test of Gastric Secretion from a Physiological Point of View, Canad. M. A. J. **23**:268, 1930.

the conditions under which the patient lives than those which are present after a powerful chemical stimulant on the gastric cells in an empty stomach.

In four patients the secretion did not respond to food or histamine. In one, free acid was present in only one sample, and in two others, in two samples extracted at the fifteen minute intervals. Histamine is one of the most powerful stimulants of secretion of hydrochloric acid known, and since, as already stated, it acts directly on the gastric cells, the most likely explanation of the anacidity is that some change occurred in the secretory cells.

What the change is or why it occurs I do not know. Sections of the fundus have been examined for many years after partial gastrectomy, and they appear normal.[18] But gastric mucosa that looks normal under the microscope may occur with achylia, and besides no specimen has been examined microscopically in which anacidity to histamine has been found after operation. Possibly a spread of the gastritis present in nearly all cases of ulcer is responsible, but as yet I do not know. Bearing on this problem is the work of Winkelstein,[19] who reported that after partial gastrectomy 55 per cent of stomachs do not excrete neutral red. Since excretion of the latter is supposed to be suppressed only in the presence of true anacidity, the presumption was that true achylia existed in those cases.

Comfort and Osterberg [20] found that 20 per cent of their subjects showed anacidity with histamine after partial gastrectomy. No report was made of the percentage of anacidity following the ingestion of food. They conclude, in view of the small proportion of anacidity with histamine, that the gastric, or secondary, phase of secretion is not of great importance. But it should be evident that this conclusion, though it may be true, is not a necessary consequence of their work. Histamine is similar to the chemical stimulant of the second phase. To use it after partial gastrectomy is to supply a stimulus similar to the one removed. The surprising thing is that any subject shows anacidity after the use of histamine, for the acid cells are still present. As already stated, it seems necessary to assume some changes in the secreting cells to account for this. Whatever the cause, there can be little doubt that it is associated with the partial gastrectomy. This unknown factor may also be partly

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18. Thus a patient operated on for gastric polyps five years after gastrectomy for ulcer showed normal mucous membrane in the stomach (microscopic examination). There was no recurrence of the ulcer.

19. Winkelstein, A.: Gastric Secretion After Partial Gastrectomy for Ulcer, Am. J. Surg. **7**:494, 1929.

20. Comfort, Mandred W., and Osterberg, Arnold E.: Gastric Secretion After Stimulation with Histamine, J. A. M. A. **97**:1141 (Oct. 17) 1931.

responsible for the progressive reduction in acidity previously reported in many cases of partial gastrectomy in which acidity was present after the operation.[7]

In conclusion I would emphasize that although it is of the utmost importance to accumulate as many facts concerning gastric secretion as possible, any comparisons of the results should be accompanied by a realization that the mechanisms involved may not be identical. It is, to mention one instance, justifiable to compare the secretion after the injection of histamine to that obtained after the ingestion of food; but the factors involved are not the same. And they are not the same because gastric secretion due to food is not the pouring out of hydrochloric acid and pepsin as a response to one type of stimulus, but a series of responses to stimuli arising from many sources, acting through different channels and effected in various ways. The era of the Ewald tests, with the examination of a single specimen after a test meal, was followed by that of the Rehfuss tests, with fractional examinations for two or three hours. Attention should now be focused on the separate phases of secretion, to study them individually in both normal and pathologic conditions.

SUMMARY AND CONCLUSIONS

Gastric secretion is the total of various distinct phases of secretion in response to stimuli acting at different points.

The three chief phases are: (1) the primary, due to reflexes from various sensory organs reaching the stomach over the vagus nerve; (2) the secondary, or gastric, due to chemical stimulation of the antrum, and (3) the intestinal. In addition to these there is the spontaneous secretion, part of which seems to be due to conditioned reflexes.

Some stimuli, such as food, excite all the phases, whereas other stimuli, such as histamine, stimulate the secreting cells directly and seem to be similar to the stimuli effecting the second phase.

The removal of one phase, as by sectioning the vagi or by removal of the antrum, leaves the other phases.

If the secretion of the remaining phases is collected in a gastric pouch (Pavlov), it is not neutralized by intestinal regurgitation, and free acid can be demonstrated. As far as I know, the concentration of hydrochloric acid secreted by the various phases is the same. If, therefore, one phase is removed and if secretion of acid persists in the pouch, there is no reason to expect the concentration of that secretion to be lowered. If the secretion is collected from the stomach the free acid may be partly or completely neutralized, producing pseudo-anacidity.

Partial gastrectomy removes the second or gastric phase. Whether anacidity results in the stomach after the ingestion of food depends on: (1) the amount of secretion which has been caused by the second phase;

(2) the amount of secretion of the other phases which are left, and (3) the amount of neutralization due to the food, intestinal regurgitation and saliva. When 3 is sufficient to neutralize 2, anacidity results. The patients show free acid after the injection of histamine.

In addition to pseudo-anacidity after partial gastrectomy for ulcer in man, a true anacidity develops in some patients. In these there is anacidity both to food and to histamine. This may be due to changes in the secreting cells themselves.

Partial gastrectomy (removal of the second phase) in a dog with a transplanted subcutaneous gastric pouch which has no nervous stimulation and hence no primary phase produces anacidity in the pouch for six hours. Prior to the gastrectomy the pouch secretes acid from the first hour. The pouch continues to respond normally to histamine.

FIFTY-FIFTH REPORT OF PROGRESS IN ORTHOPEDIC SURGERY

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NEOPLASMS

Tumors of Bone.—Brailsford [25] pointed out that while the "barrier action" of the epiphyseal cartilage to bacteria and tumor cells is great, the breaking down of the barrier by a destructive lesion, as demonstrated by a roentgenogram, does not necessarily indicate that the lesion is malignant, as lesions of a tuberculous nature frequently act in this manner.

Radiosensitivity of Tumors.—Stewart [26] reviewed extensively the relative radiosensitivity of benign and malignant tumors. This article, replete with the experiences of the author, merits reading. The tumors were discussed according to their tissue origin.

Review of Ewing's Tumor.—Lattman [27] stated that Ewing's tumor should be diagnosed on the basis of the history of the clinical and roentgenologic findings and, above all, of the radiation therapeutic test. Biopsy was deprecated on the grounds that early metastases may follow. The tumor, which is most common in males under 30 years of age, is usually situated in the middle of the bone and never in the epiphyses. While there is occasionally a formation of new bone, normally the tumor causes definite destruction of the cortical and central portions of the

25. Brailsford, J. F.: Brit. J. Radiol. **7**:233, 1934.

26. Stewart, F. W.: Radiosensitivity of Tumors, Arch. Surg. **27**:979 (Dec.) 1933.

27. Lattman, I.: Brit. J. Radiol. **7**:194, 1934.

bone. Irradiation is the most satisfactory form of treatment, and amputation should be reserved for cases in which the condition of the soft tissues precludes further irradiation or in which pain is unbearable.

Benign Giant Cell Tumor of Bone.—Holland [28] expressed the opinion that the roentgenologic appearance of a benign giant cell tumor of bone, i. e., a self-contained uniform expansion, an area of internal destruction and the shadows of the bony trabeculae, is insufficient to warrant a definite diagnosis, but that a long history is of assistance in making a diagnosis. He cited five cases of the tumor in unusual locations: in the shaft of the fibula, in the shaft of the humerus, in a rib, in the ischial tuberosity and in the patella.

Roentgenologic Characteristics of Echinococcus Disease in Bone.—Claessen [29] reported four more cases of echinococcus disease of bone and reviewed those that had previously been reported in the medical literature. He expressed the opinion that sporadic cases may be found anywhere and that a knowledge of the roentgenologic appearance is important, since from 1 to 2 per cent of cases of echinococcus disease appear in bone. One third of these cystic tumors are found in the pelvis; the spinal column is next in frequency of involvement. In the author's cases, the disease was found in the iliac bone, in the sacrum, in the head of the femur and in the diaphysis of the femur and of the fibula. In bone, the cyst is not surrounded by a strong fibrous capsule. There is practically no regional atrophy of bone and no periosteal reaction. The appearance is that of an expansive growth extending from the centrum outward. The limits of the disease can rarely be determined by roentgen examination.

MISCELLANEOUS

Synovial Sheaths and Fascial Spaces of the Hand.—Three excellent drawings of dissections demonstrating the topographic anatomy of the hand were shown by Hughes-Jones.[30] Their value is enhanced by the fact that the palmar creases are superimposed, which gives an easy means of locating the position of the synovial sheaths and the fascial spaces.

Improved Technic for Examination of the Shoulder.—A method of obtaining a satisfactory roentgenogram of the shoulder was described by Fergusson.[31] First, the patient is placed in a supine position on a Potter-Bucky diaphragm, with the uninjured shoulder raised by pads. The film is suitably centered. The rays actually passing through the glenoid fossa are oblique. Next, the patient is helped over into an

28. Holland, C. T.: Brit. J. Radiol. **7**:277, 1934.
29. Claessen, G.: Acta radiol. **15**:178, 1934.
30. Hughes-Jones, W. E. A.: M. J. Australia **2**:658, 1933.
31. Fergusson, J. N.: Brit. J. Radiol. **7**:33, 1934.

almost prone position, the uninjured shoulder again being raised by pads. The film, placed as before, caused the oblique rays to pass through the scapula so that the bone appears scarcely broader than its axillary border. A kilovoltage of about 65 is used for the first film, and of 80 for the second. A less satisfactory result can be obtained by the use of an erect Potter-Bucky diaphragm, with the patient in the upright position.

Osteochondritis Dissecans: Intra-Articular, Osteocartilaginous Loose Bodies.—Conway [32] based his discussion on observations on ten cases of osteochondritis dissecans. The well known theories of étiology —trauma (acute or due to faulty bearing of weight), infection and mycotic embolism—were discussed. The pathologic aspects and the symptoms were dealt with. The knee was involved in eight cases and the elbow in two, which is, roughly, the usual ratio. The loose bodies usually arise in the knee, from the lateral portion of the internal condyle. They may arise from the patella or may be synovial chondromas. The best time for the removal of the loose body is during the period of demarcation before synovial change has occurred.

Posttraumatic Acute Bone Atrophy (Sudeck's Atrophy).—Gurd [33] discussed acute atrophy of bone, which may be trivial, but which usually occurs with injury near a joint. The atrophy involves the small bones of the hands and feet more frequently than the shafts of long bones. The author offered the explanation that the cause of the condition is a stimulus of the reflex arc, with secondary local hyperemia and absorption of bone. The cure may be slow, but diathermy is of value, and in the treatment of weight-bearing joints, protected weight bearing in plaster is most important in speeding recovery.

ORTHOPEDIC OPERATIONS

Treatment of Pyogenic Osteomyelitis of the Sacro-Iliac Joint by the Bardenheuer-Picque Resection, Modified by the Orr Method.—Kulowski,[34] from a review of thirty cases of pyogenic sacro-iliac infection seen in Steindler's clinic, concluded that results by any method other than resection of the joint are poor because of inadequate drainage. He reported in detail four cases in which the patient was treated by complete or partial resection of the joint by the Bardenheuer-Picque technic. The posterior half of the ilium was exposed subperiosteally, both intrapelvically and extrapelvically, carrying the exposure down to the sciatic notch. The ilium was then sectioned vertically through both tables, and the flap levered out by driving a chisel into the sacro-iliac joint. The resection in some instances was partial, a bridge of bone being left just above

32. Conway, F. M.: Ann. Surg. **99**:140, 1934.
33. Gurd, F. B.: Ann. Surg. **99**:449, 1934.
34. Kulowski, J.: Am. J. Surg. **23**:305, 1934.

the sciatic notch; in others the posterior part of the ilium was removed. The sacral cartilage and necrotic bone were then removed with a chisel and a curet until normal bone was reached. Any intrapelvic abscess was evacuated by blunt dissection in the depths of the wound. The wound was then loosely packed with petrolatum gauze, and the pelvis was immobilized in a double plaster spica. In the last four cases in which this treatment was used there were no deaths, but sufficient time has not elapsed for a final study of the end-results.

End-Results of Arthroplasties of the Hip.—Campbell, in 1927, reported a study of the end-results of arthroplasties of the hip. With the increased experience and further study which the lapse of time has afforded, he reported [35] a total of one hundred and twenty-seven arthroplasties done on ninety-four patients. The operation consisted of the remodeling of the acetabulum and the head of the femur and the interposition of a double layer of fascia lata. He used the Smith-Petersen approach, being most careful not to strip off the soft tissues from the neck of the femur, so preserving its blood supply and preventing aseptic necrosis. He permitted walking after from four to six weeks if roentgenograms showed satisfactory bone structure. He concluded that arthroplasty should be undertaken in cases of nonarticular disease of the hip which has become quiescent. Exceptions are made in presons with tuberculosis or unsettled compensation and in the cases of men doing heavy labor. He considered treatment in bilateral cases to be much more difficult, the end-results on the whole being unsatisfactory, but he expressed the belief that more careful study might yield better results. Of forty-four nonarticular cases with known end-results, in 60 per cent the results were excellent and in 22 per cent, good; in 18 per cent the results were poor or there was failure.

Results of Operative Treatment of Wry Neck.—Arnold [36] analyzed the end-results following operative procedures for wry neck in the clinic at Danzig. Four methods of correction were reviewed: subcutaneous tenotomy, open tenotomy, open division of the muscle and total or partial extirpation of the muscle. The best functional and cosmetic results were obtained following open tenotomy of the sternocleidomastoid muscle at the mastoid process, with full correction of the deformity and painstaking after-care. For patients over 15 years of age, or for those, particularly males with very severe cases, total or partial extirpation of the muscle was recommended.

FRACTURES

Treatment of Fractures of the Upper End of the Humerus.—After studying the mechanics of the shoulder joint on a skeleton to which

35. Campbell, W. C.: J. Michigan M. Soc. **33**:49, 1934.
36. Arnold, W.: Arch. f. klin. Chir. **178**:257, 1934.

artificial elastic muscles has been attached, Howard and Eloesser [37] reached several interesting conclusions. The much used abduction treatment of fractures of the surgical neck of the humerus is wrong, theoretically and clinically. The displacement of the distal fragment is produced by the abductor muscles of the shoulder, the latissimus dorsi, the teres major and the pectoralis major. Abduction of the arm increases the pull of these muscles. The authors concluded that if the long head of the biceps is intact, fractures of the surgical neck of the humerus may be reduced most readily by traction on the arm in a neutral position (not abducted), with a simultaneous manual manipulation of the distal fragment. If the long head of the biceps is ruptured open, operation should be resorted to if satisfactory reduction is to be accomplished. After reduction, the most stable position of the fracture is with the arm bandaged to the body over a small axillary pad.

Reduction of Fractures of the Surgical Neck of the Humerus.—In cases of fracture of the surgical neck of the humerus which have resisted the normal methods of setting, Anderson [38] advocated that the proximal fragment be controlled by a bone-awl, which is introduced through a stab wound on the outer aspect of the shoulder and partially transfixes the bone. Subsequent steps are carried out under the fluorescent screen. Traction is exerted in the line of the arm, and while the traction is maintained the arm is adducted across the chest. The abducted upper fragment is then brought into apposition by depressing the bone-awl. Last, the arm is brought slowly to a slightly abducted position.

Treatment of Fractures of the Radius and Ulna: New Anatomic Method of Treatment.—Anderson [39] has devised a special form of portable apparatus for skeletal traction and countertraction for the reduction of fractures of the forearm. The apparatus consists of a duralumin frame with a horseshoe base at either end. One pin was passed through the upper end of the ulna, and a half-pin is passed into, but not through, the lower end of the radius. An aluminum cuff fits over the ulnar side of the forearm to prevent rotation. Rotation of either the upper or the lower fragment can be produced by turning either horseshoe base. The apparatus can be modified to care for fractures of the lower end of the humerus or of the olecranon. After the reduction is complete the arm is incorporated in a cast at a right angle.

Fracture of the Tibial Spine.—Venable [40] stated that the usual cause of fracture of the tibial spine is a pull of a strong cruciate ligament

37. Howard, N. J., and Eloesser, L.: J. Bone & Joint Surg. **16**:1, 1934.
38. Anderson, H. M.: Brit. M. J. **1**:232, 1934.
39. Anderson, R.: J. Bone & Joint Surg. **16**:379, 1934.
40. Venable, C. S.: Am. J. Surg. **24**:478, 1934.

when the leg is fixed and the body is rotated or when the body is fixed and the lower part of the leg rotated. The clinical signs are extreme pain, rapid bloody effusion of the knee joint and limitation of motion. Prompt removal, he stated, is the only way to prevent deformity, and there is little, if any, disturbance of stability in the knee after such a procedure.

[ED. NOTE.—Removal of the fractured tibial spine is not always necessary. Open reduction has given a good result in the experience of the editors.]

Treatment of Compound Fractures of the Tibia.—Simpson-Smith [41] gave an account of a method of treating compound oblique or transverse fractures of the tibia which he had carried out in twenty cases. After preparation of the leg, an incision 5 inches (12.7 cm.) long was made, a thorough débridement was carried out and the wound was washed with acriflavine hydrochloride. The periosteum was not opened, but the subcutaneous surface and anterior and postero-internal borders of the tibia were cleared for 1 inch (2.5 cm.) above and below the fracture. The fragments were brought into line by the traction of an assistant on the foot and the use of Lane's forceps. A special clamp which gripped the exposed borders was applied, and before it was tightened the fragments were thrust home. A sterile gauze roll was next applied, covering the wound and surrounding the clamp. A skin-tight sterilized plaster case was applied from the middle of the thigh to the toes, the foot being slightly flexed in a plantar position. When the plaster was dry, a window was cut to expose the wound, and the clamp was removed. The wound was sutured, with the exception of a small portion at the bottom. After six weeks or longer the plaster was removed, a short plaster cast with a Böhler's walking iron was applied and the patient was encouraged to walk with it for a few more weeks, by which time the union was firm.

Absorbable Metallic Material in Bone Surgery.—Verbrugge [42] treated twenty-one fractures in various parts of the body with magnesium bolts, screws or staples, as the case demanded. The material was completely absorbed, but the process was slow enough to permit the formation of callus. Small amounts of magnesium were absorbed in three or four months, and larger amounts lasted correspondingly longer. No trace of metal was found after two years, but in many cases the exact time of its disappearance was unknown. Absorption was accompanied by the production of hydrogen, which caused no symptoms. No toxic or irritating symptoms were observed. The maximum amount of magnesium introduced was 5 Gm.

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41. Simpson-Smith, A.: Brit. M. J. **2**:1019, 1933.
42. Verbrugge, J.: Presse méd. **42**:460, 1934.

RESEARCH

Investigation on the Osseous System of the New-Born.—Toverud [43] analyzed the skull bones and ribs of one hundred infants who died at or shortly after birth. He found a subnormal amount of ash and a low calcium content in the bones of infants whose mothers had received an insufficient amount of food during pregnancy. The calcium content was depleted more than the phosphorus content. More marked depletion was shown in premature infants or in twins born of malnourished mothers. There was an increase in the osteoid tissue, with small osteocytes and a lack of intercellular substance in the children of malnourished mothers. Toverud expressed the opinion that these changes are closely related to the osteoporosis and rickets seen during early postnatal life.

Effect of Low Calcium Content on Osteogenesis and Healing of Fractures.—Key [44] resected bone from the ulnas of twenty dogs. One side was used as a control. In the defect on the other side, various substances containing calcium were introduced, and the process of healing was followed both by roentgen examination and by subsequent inspection of the lesions. Key concluded that neither calcium phosphate and carbonate in the proportions in which they occur in bone nor bone powder, made by removing the organic matter from bone, appeared to stimulate osteogenesis of bone when implanted in a bone defect.

Small Bone Grafts.—Keith [45] transplanted small bone grafts into defects in the radius in young and adult dogs. In one series, chips of bone were placed about and between the end of the bone, a section of bone and periosteum having been removed. In four experiments there was almost complete bridging of the gap in from twenty to thirty-five days. Union was often more definite at the proximal end than at the distal end. Mild weight bearing was considered favorable to union. It was considered unwise to fragment a bone graft more than necessary, since to do so destroys somewhat its supporting and osteogenic functions. The formation of new bone from the grafts was much more marked in young than in adult dogs, and this tendency was dependent on the presence of living osteogenic cells in the grafts. It was emphasized that an intact blood supply of the bed of the graft and the combined layer of the periosteum is important. From the experiments there is no evidence that metaplasia of other connective tissue cells to bone-forming cells plays a part in the formation of new bone associated with bone grafting.

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43. Toverud, K. V.: Ztschr. f. Kinderh. **56**:56, 1934.
44. Key, J. A.: J. Bone & Joint Surg. **16**:176, 1934.
45. Keith, W. S.: J. Bone & Joint Surg. **16**:314, 1934.

Experimental Transplantation of Bone with Special Reference to the Effect of Decalcification.—Ghormley and Stuck [46] reviewed extensively the literature on the transplantation of bone and carried out experiments on adult dogs which seemed to show that the best fusion of the bone transplant to surrounding bone resulted when a cancellous graft removed either from the iliac crest or from the tibia was used. Cortical grafts did not die but showed diminished condensation, and pure periosteal transplants did not form new bone. The authors speculated that in young animals, or in children, periosteum may produce new bone when transplanted. Bone chips alone, as used in the Hibbs method of spinal fusion, gave good fusion, but not as good as that produced by the cancellous graft. Animals placed on a decalcifying diet prior to the transplantation of bone gave evidence of more active production of new bone both around the cortical and around the cancellous transplants.

Experimental Studies of Reparative Costal Chondrogenesis and Transplanted Bone.—Bisgard [47] demonstrated in patients in whom the costal cartilages had been resected, and also in dogs, that the perichondrium has little if any power to regenerate cartilage. He therefore advocated the immediate transplantation of osteoperiosteal grafts to the chondrectomized perichondral beds to bridge the gap from the rib to the sternum.

Experimental Tuberculosis of the Bones and Joints in Rabbits.—Trudel [48] was able to produce tuberculous infection in rabbits by the injection of a suspension of tubercle bacilli into the nutrient artery of the femur. A typical tuberculous condition developed in the knee joints in the majority of the animals, provided the animals had been sensitized to tuberculosis previously. Otherwise, the animals either recovered or died of generalized tuberculosis. In 75 per cent of the sensitized animals, Trudel found that after the bone lesion developed there was no other detectable focus.

[ED. NOTE.—This work is of greatest importance, because it shows again that tuberculous lesions of the bone are rarely, if ever, the primary lesion, although the primary lesion may be healed.]

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46. Ghormley, R. K., and Stuck, W. G.: Experimental Bone Transplantation, with Special Reference to Effect of "Decalcification," Arch. Surg. **28**:742 (April) 1934.

47. Bisgard, J. D.: Surg., Gynec. & Obst. **58**:817, 1934.

48. Trudel, P. J.: Am. Rev. Tuberc. **28**:331, 1933.